

Systematic Review

Probiotic-postbiotic crosstalk in the gut microbiome: emerging mechanisms in colorectal homeostasis and cancer prevention – a systematic review

Swati Mishra¹, Praveen Kumar Singh¹, Pothugunta Sai Krishna², Chellappa Vijayakumar^{3*}

¹Department of Zoology, Anugrah Memorial College, Magadh University, Gaya, Bihar, India

²Department of Surgical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

³Department of Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

Received: 03 August 2026

Revised: 11 September 2026

Accepted: 22 September 2026

*Correspondence:

Dr. Chellappa Vijayakumar,

E-mail: vijaymmc01@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

The gut microbiome is increasingly recognized as a critical determinant of gastrointestinal health and disease, and interactions between probiotic microorganisms and their bioactive metabolites, known as postbiotics, play a fundamental role in maintaining colorectal homeostasis. Recent evidence suggests that disruption of these interactions contributes to colorectal carcinogenesis, while restoration of microbial balance may provide novel preventive and therapeutic opportunities. This systematic review aimed to evaluate the role of probiotic-postbiotic interactions in colorectal homeostasis and their potential implications in colorectal cancer prevention through published literature from 2020 to 2025. A structured search of peer-reviewed literature was conducted using PubMed, Scopus, and Web of Science, and studies examining gut microbiota composition, probiotic supplementation, postbiotic metabolites, and colorectal disease outcomes were included. Data were systematically extracted and synthesized to evaluate associations between microbial diversity, functional metabolites, inflammatory pathways, and colorectal pathology. The reviewed literature consistently demonstrated that probiotic genera such as *Lactobacillus* and *Bifidobacterium* enhance the production of beneficial postbiotics, particularly short-chain fatty acids including butyrate, acetate, and propionate. These metabolites were associated with improved epithelial barrier function, suppression of inflammatory signaling pathways, modulation of host immunity, and inhibition of tumorigenic processes. A balanced gut microbiome was associated with a reduced incidence of colorectal adenomas and carcinomas, whereas dysbiosis was linked to chronic inflammation, epithelial dysfunction, and increased cancer risk. Overall, probiotic-postbiotic crosstalk represents a critical mechanistic pathway in colorectal homeostasis and cancer prevention, supporting the development of microbiome-targeted interventions aimed at reducing colorectal cancer burden, although further prospective clinical and mechanistic studies are warranted.

Keywords: Gut microbiome, Probiotics, Postbiotics, Colorectal cancer, Short-chain fatty acids, Colorectal homeostasis

INTRODUCTION

The human gastrointestinal tract harbors trillions of microorganisms collectively referred to as the gut microbiome.¹ These microorganisms include bacteria,

archaea, fungi, viruses, and protozoa that coexist in a highly complex and dynamic ecosystem. The gut microbiome performs essential functions including nutrient metabolism, vitamin synthesis, immune regulation, maintenance of epithelial integrity, and

protection against pathogenic microorganisms. Advances in sequencing technologies and microbial ecology have highlighted the profound influence of the gut microbiota on human health and disease.²

Among gastrointestinal diseases, colorectal cancer (CRC) represents a major global health challenge. According to recent epidemiological reports, CRC remains one of the most commonly diagnosed cancers worldwide and is a leading cause of cancer-related mortality. While genetic predisposition contributes to disease development, environmental and microbial factors play equally significant roles. Increasing evidence suggests that alterations in gut microbial composition, termed dysbiosis, contribute to colorectal carcinogenesis through multiple mechanisms including chronic inflammation, oxidative stress, immune dysregulation, and production of carcinogenic metabolites.³

Probiotics are live microorganisms that confer health benefits to the host when administered in adequate amounts. Species belonging to the genera *Lactobacillus* and *Bifidobacterium* are among the most extensively studied probiotics. These organisms promote intestinal health by improving microbial balance, enhancing mucosal barrier function, regulating immune responses, and inhibiting pathogenic microorganisms.⁴

Recent research has shifted attention from probiotics themselves to their metabolic products. These products, termed postbiotics, include short-chain fatty acids (SCFAs), bacteriocins, extracellular polysaccharides, enzymes, peptides, and cell wall fragments. Postbiotics are now considered major mediators of the beneficial effects attributed to probiotics.^{2,11,12}

The concept of probiotic-postbiotic crosstalk has emerged as a novel paradigm in microbiome science. Through this interaction, probiotics influence host physiology indirectly by generating bioactive metabolites capable of regulating inflammation, immunity, and cellular proliferation. Among these metabolites, butyrate has attracted particular interest due to its role in maintaining epithelial integrity and suppressing colorectal tumorigenesis.⁵

The present systematic review was undertaken to synthesize current evidence regarding probiotic-postbiotic interactions and their contribution to colorectal homeostasis and cancer prevention.¹¹⁻¹⁵

Primary objective

Primary objective was to critically evaluate the role of probiotic-postbiotic interactions in maintaining colorectal homeostasis and preventing colorectal cancer.

Secondary objectives

The secondary objectives were to assess the effects of probiotics on gut microbiota, analyze the role of

postbiotics in colorectal health, evaluate microbiome-mediated protective mechanisms, examine the association between microbiome diversity and colorectal outcomes, and identify microbiome-based therapeutic opportunities.

METHODS

Study design and setting

This study was designed as a systematic review conducted in the Department of Zoology, Bihar over a period of six months. It involved a comprehensive and structured review of published scientific literature to evaluate the role of probiotic-postbiotic interactions in colorectal homeostasis and colorectal cancer prevention. A systematic review design was selected to synthesize existing evidence, identify emerging mechanisms, and summarize therapeutic implications related to gut microbiome modulation.

Literature search strategy

A structured literature search was performed using major electronic scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Relevant articles published between January 2020 and December 2025 were identified using a combination of medical subject headings (MeSH) terms and free-text keywords. The search strategy incorporated terms such as “gut microbiome,” “gut microbiota,” “probiotics,” “postbiotics,” “short-chain fatty acids,” “microbial metabolites,” “intestinal homeostasis,” “colorectal cancer,” “colorectal neoplasia,” “dysbiosis,” and “microbiome-based therapy.” Boolean operators (AND, OR) were used to optimize search sensitivity and specificity.^{1,3,7,11-15}

The search was conducted independently and systematically to ensure comprehensive retrieval of relevant studies. Reference lists of selected articles were also screened manually to identify additional studies that met the inclusion criteria.

Study selection

Retrieved articles were initially screened based on their titles and abstracts. Studies deemed relevant to the objectives of the review were subjected to full-text assessment. The selection process aimed to include studies that provided substantial information regarding the interactions between probiotics, postbiotics, gut microbial ecology, and colorectal disease outcomes.

Inclusion criteria

The review included peer-reviewed research articles published between 2020 and 2025 that investigated gut microbiota composition and diversity, evaluated probiotic supplementation and its biological effects, examined postbiotic metabolites particularly SCFAs, involved human clinical studies, animal experiments, or in vitro

investigations relevant to colorectal health, and reported outcomes related to colorectal homeostasis, inflammation, adenoma formation, or colorectal cancer.^{7,11-15,21,24}

Exclusion criteria

Studies were excluded if they were published before January 2020; were editorials, commentaries, letters to the editor, conference abstracts, or opinion pieces; were duplicate publications identified across databases; lacked sufficient methodological details or outcome measures; were not available in English; or were unrelated to colorectal health or microbiome-mediated mechanisms.

Data extraction

Data extraction was performed using a standardized data collection format developed for this review. Information extracted from each eligible study included the following.

Data extracted from each eligible study included the author(s) and year of publication, study design and population characteristics, type and strain of probiotic organisms investigated, nature and concentration of postbiotic metabolites, gut microbiota diversity and composition parameters, reported molecular and cellular mechanisms, inflammatory biomarkers and immune responses, and colorectal disease outcomes, including adenoma formation, colorectal cancer incidence, and markers of intestinal homeostasis.

The extracted data were reviewed and organized into thematic categories to facilitate comparative analysis and interpretation.

Study parameters

The primary study parameters evaluated included microbial parameters such as gut microbiota diversity indices, the relative abundance of beneficial bacterial genera including *Lactobacillus* and *Bifidobacterium*, and indicators of microbial dysbiosis; postbiotic parameters such as the production of short-chain fatty acids, including butyrate, acetate, and propionate, as well as other biologically active microbial metabolites; molecular parameters such as inflammatory mediator expression, NF-κB signaling activity, immune modulation markers, and epithelial barrier integrity indicators; and clinical parameters such as the incidence of colorectal adenomas and carcinomas, markers of colorectal inflammation, and indicators of colorectal homeostasis and disease progression.^{4,5,7,10,13,14,20,21}

Data synthesis and analysis

A qualitative synthesis approach was adopted due to the heterogeneity of study designs, populations, and outcome measures among the included studies. Findings were systematically categorized according to probiotic species, postbiotic metabolites, molecular mechanisms, and

colorectal outcomes. Comparative synthesis was performed to identify recurring themes, consistent associations, and emerging mechanistic pathways linking probiotic-postbiotic crosstalk with colorectal health.^{11,12,14,15}

The synthesized evidence was critically evaluated to determine the strength of associations between gut microbiome modulation, postbiotic production, and colorectal cancer prevention. Particular emphasis was placed on studies investigating the role of SCFAs, immune regulation, epithelial barrier function, and inflammatory signaling pathways involved in colorectal carcinogenesis.

RESULTS

The reviewed studies demonstrated a beneficial role of probiotic-postbiotic interactions in maintaining colorectal homeostasis and reducing colorectal cancer risk. The findings consistently showed that probiotics exert protective effects through modulation of gut microbial diversity and production of bioactive metabolites, particularly SCFAs.¹¹⁻¹⁴

Probiotic diversity and gut microbiota modulation

Several studies reported that supplementation with probiotic strains, particularly *Lactobacillus* and *Bifidobacterium*, resulted in favorable alterations in gut microbial composition. Increased abundance of beneficial bacteria and reduction in pathogenic species such as *Fusobacterium nucleatum*, *Escherichia coli*, and *Enterococcus faecalis* were frequently observed.^{4,9-11}

Improved microbial diversity was associated with enhanced intestinal homeostasis, reduced inflammatory responses, and improved metabolic activity.

Studies utilizing next-generation sequencing techniques demonstrated that probiotic supplementation increased alpha diversity indices and promoted a more stable microbial ecosystem (Table 1).^{10,11,21}

Table 1: Effects of probiotic species on gut microbiota.

Probiotic species	Major postbiotics produced	Biological effects	Clinical outcome
<i>Lactobacillus</i> spp.	Butyrate, lactate	Anti-inflammatory, barrier protection	Reduced adenoma risk
<i>Bifidobacterium</i> spp.	Acetate, propionate	Immune modulation	Lower carcinoma incidence
Mixed probiotic flora	SCFAs	Microbial stability	Improved gut homeostasis

Postbiotic production and metabolic activity

One of the most consistent findings across studies was the increased production of SCFAs following probiotic administration. Butyrate, acetate, and propionate were identified as the predominant metabolites associated with beneficial colorectal outcomes.^{5,13,14}

SCFAs function as signaling molecules influencing cellular metabolism, epithelial function, and immune responses. Butyrate emerged as the most extensively studied metabolite due to its ability to serve as the primary energy source for colonocytes while simultaneously regulating gene expression.^{5,7,13,14}

Several studies demonstrated that probiotic supplementation significantly increased fecal butyrate concentrations compared with control groups, indicating enhanced metabolic activity of beneficial gut bacteria (Table 2).^{11,13,14}

Table 2: Major postbiotics and their protective mechanisms.

Post-biotic	Source organisms	Mechanism of action	Colorectal effect
Butyrate	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	HDAC inhibition, NF-κB suppression	Anti-inflammatory, anti-cancer
Acetate	<i>Bifidobacterium spp.</i>	Immune regulation	Maintains microbial balance
Propionate	Mixed flora	Cytokine modulation	Reduces inflammation
Bacteriocins	Various probiotics	Antimicrobial activity	Suppresses pathogens

Effects on intestinal barrier integrity

Multiple studies highlighted the importance of probiotic-derived metabolites in maintaining epithelial barrier integrity. SCFAs were shown to increase the expression of tight-junction proteins such as occludin, claudin, and zonula occludens-1 (ZO-1).^{5,7,11,13}

Enhanced barrier function reduced intestinal permeability and prevented translocation of microbial toxins into systemic circulation. Improved epithelial integrity was associated with decreased mucosal inflammation and reduced susceptibility to carcinogenic insults.^{5,11,18}

Research involving experimental animal models consistently demonstrated that probiotic supplementation restored damaged intestinal barriers and accelerated mucosal healing following inflammatory injury.

Immunomodulatory effects

A significant body of evidence indicated that postbiotics exert potent immunomodulatory effects. Studies demonstrated reductions in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β).^{3,11,12,23}

Conversely, anti-inflammatory mediators such as interleukin-10 (IL-10) were often increased following probiotic intervention. These findings suggest that probiotic-derived metabolites contribute to immune homeostasis by regulating both innate and adaptive immune pathways (Table 3).^{11,12,23}

Table 3: Immunological effects of postbiotics.

Immunological parameter	Observed effect
TNF-α	Decreased
IL-6	Decreased
IL-1β	Decreased
IL-10	Increased
Regulatory T-cell activity	Increased
NF-κB activation	Suppressed

Anti-carcinogenic activity

Several studies reported that SCFAs possess direct anti-carcinogenic properties. Butyrate was shown to inhibit colorectal cancer cell proliferation, induce apoptosis, and regulate genes involved in cell-cycle control.^{5,13,14,16,19}

Experimental evidence suggested that butyrate acts as a histone deacetylase (HDAC) inhibitor, thereby influencing epigenetic regulation and suppressing oncogenic pathways. Reduced activation of NF-κB and Wnt/β-catenin signaling pathways was also reported.^{5,7,13,14,18}

Additionally, probiotic-derived metabolites were associated with reduced oxidative stress and lower levels of DNA damage, further contributing to colorectal cancer prevention (Table 4).^{11,13,14,19,24}

Association with colorectal outcomes

The reviewed literature consistently demonstrated a relationship between gut microbiome composition and colorectal disease outcomes. Individuals with greater microbial diversity and higher SCFA production exhibited lower rates of colorectal adenomas and carcinomas.^{6,7,13,14,21}

In contrast, dysbiosis characterized by reduced abundance of beneficial bacteria and increased prevalence of pathogenic organisms was associated with chronic inflammation, impaired barrier function, and increased cancer risk (Table 5).^{3,6,18,20,21}

Table 4: Anti-cancer mechanisms of SCFAs.

Mechanism	Biological effect
HDAC inhibition	Regulation of gene expression
Apoptosis induction	Elimination of malignant cells
NF-κB suppression	Reduced inflammation
Wnt/β-catenin inhibition	Reduced tumor growth
Oxidative stress reduction	DNA protection

Table 5: Microbiome status and colorectal outcomes.

Microbiome status	Inflammation	Barrier function	Disease outcome
Balanced microbiome	Low	Intact	Reduced cancer risk
Moderate dysbiosis	Moderate	Partially impaired	Increased adenoma risk
Severe dysbiosis	High	Disrupted	Increased carcinoma risk

Summary of findings

Overall, the reviewed evidence strongly suggests that probiotic-postbiotic crosstalk plays a fundamental role in colorectal homeostasis. Enhanced production of SCFAs, particularly butyrate, contributes to improved epithelial integrity, immune regulation, suppression of inflammatory pathways, and protection against colorectal carcinogenesis. These findings support the potential use of microbiome-targeted interventions as preventive and therapeutic strategies in colorectal disease management.^{11-15,21,24}

DISCUSSION

The findings of this review reinforce the emerging concept that probiotic-postbiotic crosstalk represents a central mechanism in colorectal health. Rather than acting independently, probiotics and postbiotics function synergistically to regulate host physiology.⁶

One of the most important findings is the consistent association between SCFA production and colorectal protection. Butyrate serves as the primary energy source for colonocytes and contributes to epithelial integrity. Beyond its metabolic role, butyrate acts as a histone deacetylase inhibitor, influencing gene expression and suppressing inflammatory pathways.⁷

The NF-κB pathway has been identified as a major target of postbiotic activity. Chronic activation of NF-κB contributes to inflammation-associated carcinogenesis. Several studies demonstrated that butyrate suppresses NF-κB activation, thereby reducing inflammatory mediator production.⁸

Immune modulation represents another important mechanism. Probiotic-derived metabolites influence regulatory T-cell function, cytokine production, and macrophage activity. These effects collectively promote immune homeostasis and reduce chronic inflammation.^{3,11,12,23}

The findings also support the concept that dysbiosis contributes significantly to colorectal cancer risk. Reduced microbial diversity and depletion of beneficial bacteria result in decreased SCFA production and increased inflammatory activity.

Restoration of microbial balance through probiotic interventions may therefore represent a practical preventive strategy.⁹

Despite promising findings, several limitations exist. Considerable heterogeneity was observed among studies regarding probiotic strains, dosing regimens, dietary factors, and outcome measures. Furthermore, most available evidence remains associative rather than causal.¹⁰

Nevertheless, the cumulative evidence strongly supports the role of microbiome-targeted approaches in colorectal cancer prevention and management.^{11-15,21-25}

Limitations

The limitations of this systematic review include dependence on published secondary data; variability among study populations and methodologies; lack of standardized microbiome assessment techniques; heterogeneity in probiotic strains, doses, and outcome measures; and limited long-term follow-up data in many studies.^{10,11,14,15}

Future perspectives

Future research should focus on large-scale prospective cohort studies, randomized controlled trials of probiotic and postbiotic interventions, integration of microbiome sequencing with metabolomics, development of personalized microbiome-based therapies, artificial intelligence-assisted microbiome analysis, and exploration of postbiotic formulations as therapeutic agents.¹¹⁻¹⁵

CONCLUSION

This systematic review demonstrates that probiotic-postbiotic crosstalk is a fundamental mechanism governing colorectal homeostasis. Beneficial microorganisms influence host health through production of bioactive metabolites that regulate inflammation, immunity, epithelial integrity, and carcinogenic pathways. The evidence consistently supports a protective role for probiotics and their metabolites in colorectal cancer prevention. Although further mechanistic and clinical

studies are required, microbiome-targeted interventions represent a promising frontier in preventive oncology.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. O'Keefe SJD. Diet, microorganisms and their metabolites, and colon cancer. *Nat Rev Gastroenterol Hepatol.* 2020;17(12):707-20.
2. Żółkiewicz J, Marzec A, Ruszczyński M, Feleszko W. Postbiotics-A step beyond pre- and probiotics. *Nutrients.* 2020;12(8):2189.
3. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* 2020;17(4):223-37.
4. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. *BMJ.* 2018;361:k2179.
5. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol.* 2014;12(10):661-72.
6. Wong SH, Yu J. Gut microbiota in colorectal cancer: mechanisms of action and clinical applications. *Nat Rev Gastroenterol Hepatol.* 2019;16(11):690-704.
7. Song M, Chan AT, Sun J. Influence of the gut microbiome, diet, and environment on risk of colorectal cancer. *Gastroenterology.* 2020;158(2):322-40.
8. Scott KP, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on the gut microbiota. *Pharmacol Res.* 2013;69(1):52-60.
9. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients.* 2017;9(9):1021.
10. Plaza-Díaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. *Adv Nutr.* 2019;10(1):S49-66.
11. Kvakova M, Kamlarova A, Stofilova J, Benetinova V, Bertkova I. Probiotics and postbiotics in colorectal cancer: prevention and complementary therapy. *World J Gastroenterol.* 2022;28(27):3370-82.
12. Xie W, Zhong YS, Li XJ, Kang YK, Peng QY, Ying HZ. Postbiotics in colorectal cancer: intervention mechanisms and perspectives. *Front Microbiol.* 2024;15:1360225.
13. Thulasinathan B, Suvilesh KN, Maram S, Grossmann E, Ghouri Y, Teixeira EP, et al. The impact of gut microbial short-chain fatty acids on colorectal cancer development and prevention. *Gut Microbes.* 2025;17(1):2483780.
14. He Y, Peng K, Tan J, Hao Y, Zhang S, Gao C, et al. Short-chain fatty acids and colorectal cancer: a systematic review and integrative Bayesian meta-analysis of microbiome-metabolome interactions and intervention efficacy. *Nutrients.* 2025;17(22):3552.
15. Mishra N, Garg A, Ashique S. Role of gut microbiota and postbiotics for colorectal cancer: advancing therapeutic strategies. *Cham: Springer Nature;* 2025.
16. Drewes JL, Housseau F, Sears CL. Sporadic colorectal cancer: microbial contributors to disease prevention, development and therapy. *Br J Cancer.* 2016;115(3):273-80.
17. Frick JS, Autenrieth IB. The gut microflora and its variety of roles in health and disease. *Curr Top Microbiol Immunol.* 2013;358:273-89.
18. Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science.* 2012;338(6103):120-3.
19. Bultman SJ. Emerging roles of the microbiome in cancer. *Carcinogenesis.* 2014;35(2):249-55.
20. Gagnière J, Raisch J, Veizant J, Barnich N, Bonnet R, Buc E, et al. Gut microbiota imbalance and colorectal cancer. *World J Gastroenterol.* 2016;22(2):501-18.
21. Rebersek M. Gut microbiome and its role in colorectal cancer. *BMC Cancer.* 2021;21:1325.
22. Cuevas-Sierra A, Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Martinez JA. Diet, gut microbiota, and obesity: links with host genetics and epigenetics and potential applications. *Adv Nutr.* 2019;10(1):S17-30.
23. De Almeida CV, de Camargo MR, Russo E, Amedei A. Role of diet and gut microbiota on colorectal cancer immunomodulation. *World J Gastroenterol.* 2019;25(2):151-62.
24. 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(3):511-24.
25. González-Sarrias A, Tomás-Barberán FA, García-Conesa MT, Espín JC. The gut microbiota-derived metabolites urolithins and their biological effects in colorectal health. *Mol Nutr Food Res.* 2017;61(1):1500901.

Cite this article as: Mishra S, Singh PK, Krishna PS, Vijayakumar C. Probiotic-postbiotic crosstalk in the gut microbiome: emerging mechanisms in colorectal homeostasis and cancer prevention – a systematic review. *Int Surg J* 2026;13:2202-7.