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Gut Microbiome Therapeutics for Colorectal Cancer: Advances in Bacteria- and Phage-Driven Interventions

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Abstract*— Colorectal cancer (CRC) remains a leading cause of cancer-related morbidity and mortality worldwide, with therapeutic efficacy frequently constrained by drug resistance, immune evasion, and systemic toxicity. A growing body of evidence highlights the gut microbiome and phageome as critical modulators of colorectal carcinogenesis, tumor progression, and responsiveness to therapy. This review presents a systematic integrative synthesis of gut microbiome-based therapeutics for CRC, with particular emphasis on bacteria- and bacteriophage-driven interventions. We have consolidated mechanistic and translational evidence on bacterial strategies including fecal microbiota transplantation (FMT), probiotic and synbiotic formulations, and engineered live biotherapeutic products (LBPs), alongside emerging bacteriophage-based approaches enabling precision targeting of CRC-associated pathobionts. Combinatorial bacteria–phage strategies and the role of multi-omics and artificial intelligence in guiding personalized microbiome-centred therapies are also examined. By bridging microbiology, immuno-oncology, and translational medicine, this review provides a structured framework for understanding how microbiome modulation can enhance therapeutic outcomes in CRC, while identifying key challenges and future directions for clinical translation.

Index Terms: ***Bacteriophage therapy, colorectal cancer, fecal microbiota transplantation, gut dysbiosis, gut microbiome, live biotherapeutic products, probiotics, tumor microenvironment.***

I. INTRODUCTION

Colorectal cancer (CRC) ranks among the three most prevalent malignancies globally and is the second most common cause of cancer-related mortality, accounting for approximately 1.9 million new diagnoses and over 930,000 deaths annually [1]. Despite significant progress in surgical techniques, cytotoxic chemotherapy regimens, targeted molecular therapies, and immunotherapy, the long-term prognosis for patients with advanced or metastatic disease remains poor. The five-year survival rate for metastatic CRC is below 15%, reflecting the profound challenges posed by therapeutic resistance, tumor heterogeneity, and systemic toxicity associated with conventional treatments [2]. These persistent limitations have intensified the search for complementary and mechanistically distinct therapeutic approaches.

The gastrointestinal tract harbors the most complex and densely populated microbial ecosystem in the human body, comprising an estimated 10^{13}–10^{14} microorganisms—including bacteria, bacteriophages, fungi, archaea, and protozoa—collectively referred to as the gut microbiome [3]. These microbial communities perform essential physiological functions including metabolism of dietary substrates, synthesis of short-chain fatty acids (SCFAs), regulation of mucosal immunity, and maintenance of epithelial barrier integrity. Disruption of this equilibrium, collectively termed gut dysbiosis, has emerged as a defining hallmark of CRC and a functionally active contributor to its pathogenesis rather than a mere consequence of tumor development.

Gut dysbiosis promotes colorectal carcinogenesis through interconnected genotoxic, inflammatory, metabolic, and immune-mediated pathways. CRC-associated microbial signatures are consistently characterized by enrichment of pathogenic taxa—notably Fusobacterium nucleatum, enterotoxigenic Bacteroides fragilis (ETBF), pks^+ Escherichia coli, and Streptococcus gallolyticus—alongside depletion of beneficial commensals such as Lactobacillus, Bifidobacterium, and Akkermansia muciniphila [4]. Mechanistically, colibactin produced by pks^+ E. coli induces DNA double-strand breaks and chromosomal instability; BFT secreted by ETBF activates STAT3 signalling sustaining chronic mucosal inflammation; F. nucleatum accelerates tumor progression by activating Wnt/β-catenin signalling and promoting immune evasion through Fap2-mediated inhibition of cytotoxic lymphocytes [5,6]. Loss of SCFA-producing commensals concurrently compromises epithelial barrier integrity and weakens antitumor immune surveillance, creating a microenvironmental landscape permissive to tumor growth.

In parallel, the gut phageome—the collection of bacteriophages constituting the viral component of the

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intestinal ecosystem—plays an underappreciated but critical role in shaping bacterial population dynamics and influencing host–microbe interactions. Metagenomic analyses have identified distinct phage signatures associated with CRC, including enrichment of phages infecting F. nucleatum, Parvimonas micra, and B. fragilis [7]. These phage-associated biomarkers demonstrate high accuracy in distinguishing CRC patients from healthy individuals across independent cohorts, suggesting that the gut virome may serve as both a diagnostic resource and a therapeutic target. The biological interplay between phages and their bacterial hosts adds regulatory complexity to the gut–tumor axis and catalyses interest in phage-based interventions as precision oncological tools.

The role of the gut microbiota in modulating immunotherapy efficacy in CRC has gained substantial attention in recent years [21]. The composition of the gut microbiome influences T-cell priming, cytokine milieu, and responsiveness to immune checkpoint inhibitors, explaining much of the inter-patient variability observed in immunotherapy trials [22]. Simultaneously, preclinical and clinical investigations have established the gut microbiota as a targetable node for interventions designed to sensitize tumors to checkpoint blockade and cytotoxic agents alike [23]. These converging lines of evidence position the gut microbiome not merely as a biomarker but as a pharmacologically tractable target in CRC—one amenable to modulation through a growing arsenal of bacteria- and phage-based therapeutic strategies.

II. MOTIVATION AND OBJECTIVE

The persistent limitations of standard-of-care CRC therapies—including multidrug resistance, dose-limiting toxicity, and heterogeneous immunotherapy responses—underscore the urgent need for complementary strategies that extend beyond direct cytotoxic targeting of tumor cells. Accumulating evidence that the gut microbiome actively modulates CRC initiation, progression, and treatment outcomes has fundamentally repositioned microbial communities as central players in oncology. The motivation for this review stems from the convergence of three major scientific trajectories: (1) mechanistic discoveries linking specific microbial taxa and phage populations to CRC pathobiology; (2) rapid advances in synthetic biology and phage engineering expanding the therapeutic toolkit; and (3) the emergence of multi-omics and computational platforms integrating complex biological datasets for personalized treatment design.

Recent reviews have highlighted the promise of native and engineered probiotics for CRC therapy [20], the microbiome's central role in tumor immunity and immunotherapy response [22], and the potential of microbiota-targeted approaches for precision oncology [23]. However, the field lacks a unified synthesis that integrates the full spectrum of bacteria- and phage-driven interventions alongside combinatorial strategies and AI-guided frameworks. This review addresses that gap, providing a structured analysis designed to serve both translational researchers and clinicians navigating the rapidly evolving microbiome-oncology landscape.

The primary objective is to critically synthesize evidence on bacteria- and phage-driven therapeutic interventions for CRC, bridging mechanistic insights with translational relevance. Six specific sub-objectives guide this synthesis: (1) characterization of gut microbiome and phageome signatures across CRC disease stages; (2) comparative evaluation of bacteria-based interventions including FMT, probiotics, and engineered LBPs; (3) assessment of bacteriophage-based precision strategies for pathobiont elimination; (4) analysis of combinatorial bacteria–phage therapeutic approaches and their synergistic mechanisms; (5) elucidation of molecular and immunological pathways through which microbiome modulation influences tumor biology; and (6) appraisal of AI-driven and multi-omics frameworks enabling personalized microbiome-based therapy.

III. STATEMENT OF CONTRIBUTION / METHODS

A. Protocol Development and Literature Search Strategy

This review adopts a structured systematic integrative methodology informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, adapted to accommodate an integrative and narrative synthesis framework appropriate for a translational research review. An a priori review protocol was developed specifying objectives, scope, eligibility criteria, and an analytical framework prior to literature screening. Inclusion and exclusion criteria were formalized using the Population–Intervention–Comparison–Outcome (PICO) framework to minimize selection bias and ensure methodological consistency across the reviewed evidence base.

A comprehensive literature search was executed across three major biomedical databases: PubMed/MEDLINE, Embase, and Google Scholar. Boolean search strategies combined three tiers of keywords: (i) disease-related terms (colorectal cancer, colorectal adenocarcinoma, colorectal tumorigenesis, CRC); (ii) microbial entities (gut microbiome, gut dysbiosis, bacteriophage, phageome, virome, F. nucleatum, B. fragilis, gut microbiota); and (iii) therapeutic strategies and mechanisms (fecal microbiota transplantation, phage therapy, probiotic, synbiotic, engineered bacteria, live biotherapeutic product, synthetic biology, CRISPR phage, immunotherapy, immune checkpoint). The search was restricted to peer-reviewed articles published in English from

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2015 onwards, with selective inclusion of foundational pre-2015 studies. A total of 236 articles were initially identified, of which 97 met eligibility criteria following title/abstract screening and full-text review. Key articles included seminal mechanistic studies, preclinical efficacy investigations, early-phase clinical trials, and systematic reviews.

B. Data Extraction and Integrative Synthesis

Data extraction was conducted using a standardized template capturing study design (preclinical vs. clinical), intervention type (bacterial, phage-based, or combinatorial), microbial or phage agents employed, therapeutic context (monotherapy vs. combination), reported biological mechanisms, immune and metabolic outcomes, and translational status. Extracted data were organized into thematic domains aligned with the six review objectives.

Given the anticipated heterogeneity across study designs, intervention platforms, and outcome measures, a qualitative thematic synthesis approach was employed rather than quantitative meta-analysis. Studies were grouped by therapeutic modality and mechanistic focus to enable structured comparative evaluation. An integrative analysis examined the interplay between microbiome modulation, immune remodelling, and tumor biology—with particular focus on immune checkpoint regulation, inflammatory signalling cascades, SCFA-mediated metabolic effects, and tumor microenvironment (TIME) remodelling. Particular attention was given to studies examining the microbiome–immunotherapy interface, given the emerging clinical relevance of microbiota manipulation as a strategy to sensitize MSS-CRC to checkpoint blockade [21]. Identified knowledge gaps, methodological limitations, and inconsistencies across studies were systematically documented to guide future research priorities.

IV. STATEMENT OF CONTRIBUTION

A. Bacteria-Based Therapeutic Strategies

1) Fecal Microbiota Transplantation:

Fecal microbiota transplantation represents one of the most comprehensive approaches for reversing tumor-promoting dysbiosis by restoring the diversity and functional composition of the gut microbial community. In preclinical CRC models, FMT from healthy donors significantly reduces tumor burden, suppresses pro-inflammatory signalling pathways, and enhances antitumor immune surveillance through depletion of CRC-enriched pathobionts and reciprocal enrichment of SCFA-producing taxa [8]. At the mechanistic level, FMT promotes tumor-infiltrating $CD8^+$ cytotoxic T lymphocytes and natural killer cells while suppressing immunosuppressive regulatory T cells (Tregs) and tumor-associated macrophages. Concurrent downregulation of IL-6/STAT3 and TGF-β signalling pathways contributes to a shift in the TIME toward immune activation. Combining FMT with selenium supplementation enhances microbial engraftment, amplifies butyrate production, and produces measurable reductions in tumor number and size beyond FMT alone [9].

Emerging clinical evidence substantiates the translational relevance of FMT in CRC management. Meta-analyses of early-phase clinical studies demonstrate that FMT combined with immune checkpoint inhibitors or anti-angiogenic agents can improve disease control rates and extend progression-free survival in patients with refractory or microsatellite-stable metastatic CRC—a population historically unresponsive to immunotherapy. These benefits are accompanied by increased microbial diversity and favourable remodelling of the TIME [10]. Therapeutic microbiota transplantation in digestive neoplasia more broadly has also shown promise in restoring immune homeostasis disrupted by malignancy and prior treatment [19], extending the potential application of FMT-based strategies beyond CRC.

2) Probiotics, Prebiotics, and Synbiotics:

Defined microbial interventions using probiotics offer a more controlled and reproducible alternative to FMT. Probiotic strains from the genera Lactobacillus, Bifidobacterium, and Clostridium butyricum attenuate intestinal inflammation, reinforce epithelial barrier integrity, and promote antitumor immunity through NF-κB suppression and enhanced SCFA—particularly butyrate—production [11]. A comprehensive review of native and engineered probiotics for CRC therapy has further highlighted that next-generation probiotic platforms can be rationally designed to express immunomodulatory or cytotoxic payloads, substantially expanding their therapeutic repertoire beyond conventional anti-inflammatory activity [20]. Clinically, C. butyricum supplementation during fluoropyrimidine- and oxaliplatin-based chemotherapy has been associated with improved tolerability and enhanced efficacy of immune checkpoint blockade via increased $CD8^+$ T-cell activity. Synbiotic formulations pairing probiotic strains with fermentable prebiotics (inulin, resistant starch) improve microbial persistence and functional output, providing more sustained therapeutic benefits.

3) Engineered Live Biotherapeutic Products:

Synthetic biology has enabled a new class of precision microbial therapeutics: engineered LBPs with genetically encoded anticancer functions. These platforms exploit the natural tumor-tropism of select bacterial species to deliver therapeutic payloads directly within the tumor microenvironment. Attenuated Salmonella typhimurium, Listeria monocytogenes, and Bifidobacterium longum have been exploited for tumor-targeted delivery owing to their preferential accumulation in hypoxic tumor regions [12]. Engineered Pediococcus pentosaceus strains producing

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anticancer peptides inhibit CRC cell proliferation via p53-dependent cell cycle arrest in preclinical models [13]. More advanced platforms incorporate genetic circuits enabling tumor-responsive cytotoxin secretion, anti-angiogenic factor expression, and localized immunostimulatory cytokine delivery. Capecitabine-loaded prebiotic nanoparticles combining gut microbiota modulation with chemotherapy represent a particularly innovative translational approach, demonstrating improved antitumor efficacy and reduced systemic toxicity compared with free drug administration [18].

B. Phage-Based Therapeutic Strategies

Bacteriophages offer a fundamentally distinct therapeutic modality defined by exquisite host specificity, self-amplification at the site of infection, and extensive capacity for genetic engineering. The natural host range of phages is typically restricted to one or a few bacterial strains, making them ideal precision tools for microbiome editing that avoids the broad-spectrum disruption associated with antibiotics. In the context of CRC, phage therapy aims to selectively eliminate oncogenic pathobionts while preserving beneficial commensal populations—addressing the dual challenge of pathobiont activity and commensal depletion that characterizes CRC-associated dysbiosis.

The bioinorganic hybrid phage system developed by Dong et al. [14] exemplifies the translational potential of engineered phage platforms. M13 phages conjugated with silver nanoparticles selectively target and eradicate F. nucleatum within colorectal tumor tissues, simultaneously reversing local immunosuppression by suppressing myeloid-derived suppressor cells (MDSCs) and promoting dendritic cell maturation and T-cell activation. These effects substantially enhance the efficacy of co-administered anti-PD-L1 checkpoint immunotherapy, highlighting the potential of phage-mediated microbiome editing as a strategy to sensitize immunotherapy-resistant CRC. Separately, targeted phage therapy against ETBF strains restores chemosensitivity to 5-fluorouracil in drug-resistant CRC models by eliminating BFT-driven resistance mechanisms [15].

Beyond direct bacterial lysis, engineered lytic phages disrupt biofilms formed by CRC-associated bacteria—a major structural mechanism of antibiotic and chemotherapy resistance. CRISPR-Cas–equipped phages represent the frontier of precision phage engineering: these constructs selectively target and delete specific virulence genes (such as fadA in F. nucleatum) rather than lysing the host cell outright, enabling gene-level editing of the tumor-associated microbiome with minimal ecological disruption [16]. Nanoparticle-encapsulated oral phage formulations and phage display–derived tumor-homing peptides further improve phage stability in the gastrointestinal environment and tumor targeting specificity. Early clinical investigations confirm the safety of orally administered phage preparations and their capacity to selectively deplete pathobionts while preserving beneficial commensals [16].

V. RESULTS

A. Comparative Therapeutic Profiles

Integrative synthesis of the evidence base reveals distinct and complementary therapeutic profiles for bacterial and phage-based interventions. FMT and probiotic-based strategies demonstrate broad ecological effects—restoring global microbial diversity, increasing SCFA production, reinforcing epithelial barrier function, and modulating systemic immune responses. These approaches are most effective when the therapeutic goal is ecosystem-level restoration rather than targeted pathobiont elimination. Engineered LBPs extend this capability by enabling tumor-localized drug delivery with reduced systemic exposure, combining the ecological benefits of bacteria-based approaches with precision pharmacological activity at the tumor–microbiome interface.

Phage-based platforms, by contrast, operate at the strain-specific level. Their narrow host range translates to high selectivity, minimal off-target disruption of commensal microbiota, and reduced risk of pan-microbiome disruption. The key quantitative findings from reviewed studies are summarized in Table I, illustrating comparative efficacy profiles and mechanistic distinctions across modalities. The emerging consensus is that no single modality comprehensively addresses the complexity of CRC-associated dysbiosis; rather, sequential or combinatorial deployment of complementary strategies offers the greatest therapeutic potential.

Table I: Comparative Overview of Microbiome-Based Therapeutic Strategies in CRC

Strategy	Primary Mechanism	Selectivity	Clinical Stage	Key Limitation
FMT	Dysbiosis reversal; immune remodelling	Low (community-wide)	Phase I/II trials	Donor variability; biosafety
Probiotics / Synbiotics	SCFA production; NF-κB suppression	Moderate (strain-level)	Clinical use	Engraftment variability
Engineered LBPs	Tumor-localized payload delivery	High (tumor-targeted)	Preclinical	Biosafety; regulatory hurdles

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Strategy	Primary Mechanism	Selectivity	Clinical Stage	Key Limitation
Phage Therapy	Pathobiont elimination; immune activation	Very high (strain-specific)	Phase I	Phage resistance; stability
Bacteria–Phage Combo	Synergistic dysbiosis correction	High	Preclinical	Sequencing optimization

B. Immune Remodelling and Tumor Microenvironment Effects

A consistent finding across reviewed studies is that microbiome-based interventions reshape the TIME in ways that potentiate antitumor responses and, critically, sensitize tumors to checkpoint immunotherapy. The gut microbiota's influence on immunotherapy efficacy in CRC operates through multiple converging pathways: microbial metabolites (particularly butyrate and propionate) modulate T-cell differentiation and function; microbial pattern-recognition through toll-like receptors shapes innate immune tone within the tumor; and specific commensal bacteria directly prime tumor-antigen-specific $CD8^+$ T-cell responses through antigen cross-presentation [21].

Bacteria-driven therapies exert primarily indirect immunomodulatory effects: butyrate produced by restored SCFA-producing taxa inhibits histone deacetylases (HDACs) in tumor-infiltrating T cells and macrophages, reducing exhaustion and promoting effector phenotypes. Simultaneously, increased epithelial barrier integrity limits bacterial translocation and the associated chronic inflammatory signalling that sustains immune suppression within tumors. The gut microbiota's role in modulating tumor immunity extends to the broader immunotherapy context: microbiome composition at treatment initiation strongly predicts ICI response in multiple tumor types, and microbiome-targeted interventions represent a clinically actionable strategy to expand the population of CRC patients who benefit from immunotherapy [22].

Phage-based interventions demonstrate more direct immune effects. F. nucleatum engages the inhibitory receptor TIGIT on NK cells and T cells via its Fap2 adhesin, effectively disarming cytotoxic immune populations. Phage-mediated elimination of F. nucleatum relieves this suppression, restoring NK and $CD8^+$ T-cell cytotoxicity. The bioinorganic phage system further modulates macrophage polarization, shifting tumor-associated macrophages from the immunosuppressive M2 phenotype toward the pro-inflammatory M1 state, thereby amplifying immune-mediated tumor clearance and enhancing checkpoint blockade efficacy [14].

C. Combinatorial Strategies and Synergistic Mechanisms

Sequential or combinatorial strategies integrating bacterial and phage-based modalities emerge as particularly promising from the reviewed evidence. A phage pretreatment step that selectively depletes dominant CRC-associated pathobionts creates an ecological niche within the gut microbiome that facilitates more effective engraftment of therapeutic bacteria during subsequent FMT or probiotic administration. Studies employing phage depletion of F. nucleatum followed by probiotic reconstitution with Lactobacillus and Bifidobacterium consortia report synergistic tumor suppression, reduced inflammatory markers, and substantially enhanced $CD8^+$ T-cell infiltration compared with either modality alone [14,16].

The rationale for sequential approaches is mechanistically coherent: pathobiont-occupied ecological niches actively resist colonization by beneficial bacteria, and phage-mediated niche clearance dramatically improves the efficiency of subsequent microbial reconstitution. This principle parallels the logic of targeted antibiotics–FMT protocols for Clostridioides difficile infection, where pre-treatment pathobiont reduction is established as critical for FMT engraftment success. Extending this paradigm to CRC represents a logical translational step, and early preclinical data support its feasibility and efficacy. Furthermore, integrating these microbiome-based strategies with conventional chemotherapy or immunotherapy—as exemplified by prebiotic nanoparticle–capecitabine combinations [18]—highlights the potential for microbiome modulation to amplify the activity of standard-of-care agents rather than replacing them.

VI. DISCUSSIONS

A. Mechanistic Synergies and Translational Challenges

The mechanistic evidence reviewed here establishes that bacteria- and phage-based interventions are not merely complementary—they operate through partially overlapping and partially distinct pathways that together address the full complexity of CRC-associated dysbiosis. Bacterial strategies rebuild the ecological foundation of a healthy gut microbiome: they restore SCFA production, reinforce mucosal immunity, and create a microenvironmental landscape less conducive to tumor growth. Phage strategies provide precision surgical intervention on specific oncogenic taxa—removing the most actively harmful microbial actors without collateral disruption to the surrounding commensal

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community. The colon cancer–microbiota nexus—characterized by complex and bidirectional interactions among tumor cells, immune cells, and commensal microorganisms—demands therapeutic strategies of equivalent complexity and specificity [23].

Despite mechanistic rationale and encouraging preclinical data, several translational challenges must be addressed before these strategies achieve mainstream clinical adoption. FMT is limited by donor-to-donor variability in microbial composition, the risk of transferring uncharacterized pathogens, and the absence of standardized engraftment metrics. Published cases of serious adverse events following FMT—including transmission of drug-resistant organisms—have heightened regulatory scrutiny, necessitating rigorous donor screening and pathogen-free preparation methods [10]. Phage therapy faces distinct obstacles: rapid development of phage resistance through receptor modification, superinfection immunity, and restriction-modification systems may limit therapeutic durability. Nanoparticle-encapsulated phage formulations partially address stability and delivery challenges but introduce manufacturing complexity and novel regulatory questions.

Engineered LBPs present arguably the most complex regulatory pathway, as genetically modified organisms intended for in vivo human use require extensive safety evaluation beyond conventional small-molecule pharmaceuticals. Horizontal gene transfer from engineered bacteria to commensal microbiota constitutes an additional biosafety concern that must be characterized in preclinical containment studies. Regulatory harmonization between existing GMO frameworks and emerging live biotherapeutic product guidelines will be essential for enabling efficient clinical translation of engineered LBP platforms.

B. The Role of Multi-Omics and Artificial Intelligence

A critical insight emerging from this synthesis is that the effectiveness of microbiome-based therapies is profoundly context-dependent—shaped by the patient's baseline microbiome composition, immune status, genetic background, and prior treatment history. This heterogeneity mandates a shift from one-size-fits-all microbiome interventions toward precision approaches guided by patient-specific biological profiles. Multi-omics integration—combining metagenomic, metaviromic, metabolomic, transcriptomic, and immunological datasets—offers the most complete picture of the gut–tumor axis for individual patients and enables identification of actionable therapeutic targets and predictive biomarkers.

Machine learning models trained on integrated multi-omics datasets have demonstrated utility in predicting FMT engraftment success, ICI response, and microbiome-based therapeutic outcomes in early-phase studies. Random forest classifiers and deep learning architectures can identify microbial signatures associated with favourable outcomes, enabling prospective patient stratification before treatment initiation. Federated learning frameworks—pooling multi-institutional datasets while preserving patient privacy—will substantially expand the training data available for predictive model development, a critical requirement given the compositional heterogeneity of the human gut microbiome across geographic and ethnic populations. As AI-driven predictive frameworks mature, they are expected to guide the rational selection and sequencing of bacterial and phage interventions at the individual patient level, transforming microbiome therapy from empirical to precision oncology.

VII. VII. CONCLUSIONS

This review presents a comprehensive integrative synthesis of bacteria- and phage-driven therapeutic strategies for colorectal cancer, consolidating mechanistic insights across FMT, probiotic and synbiotic formulations, engineered LBPs, precision bacteriophage systems, and combinatorial approaches. The central conclusion is that the gut microbiome constitutes not merely a diagnostic biomarker but a functionally active and pharmacologically tractable target in CRC—one whose modulation can complement, potentiate, and in some contexts overcome resistance to conventional therapies. The additional dimensions of gut microbiota–immunotherapy interactions [21,22] and the targeted microbiota approach in precision oncology [23] further underscore that microbiome modulation is not peripheral to CRC treatment but constitutes an emerging central pillar of its management.

The comparative analysis presented here highlights important mechanistic distinctions: bacteria-based approaches achieve broad ecological restoration and systemic immune remodelling, while phage-based interventions enable strain-level precision that minimizes off-target microbiome disruption. Critically, these modalities are not mutually exclusive—sequential phage-mediated pathobiont depletion followed by bacterial reconstitution emerges as a mechanistically coherent next-generation strategy that exploits the strengths of both approaches while mitigating their individual limitations. The integration of microbiome modulation with chemotherapy [18] and immunotherapy represents a particularly fertile area for future translational investigation.

Key challenges remain. Standardization of FMT preparation and donor selection, development of phage resistance management strategies, rigorous biosafety characterization of engineered LBPs, and establishment of clear regulatory pathways for advanced microbiome therapeutics are essential prerequisites for clinical translation. Progress on these fronts will require coordinated efforts spanning microbiology, oncology, synthetic biology, regulatory science, and computational medicine. The

expanded evidence base now available—including insights from microbiota transplantation in digestive neoplasia [19] and comprehensive probiotic engineering reviews [20]—provides a substantially stronger foundation for clinical trial design than existed even three to four years ago.

Looking forward, the integration of patient-specific multi-omics profiling with AI-driven predictive frameworks holds the greatest promise for transforming microbiome-based interventions from experimental tools into clinically actionable precision therapies. As these technological and scientific foundations mature, the insights synthesized in this review are expected to inform the rational design of future experimental studies and the development of evidence-based clinical protocols that harness the gut microbiome as a modifiable and therapeutically powerful axis in colorectal cancer management.

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