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Review

Probiotic-Mediated Immune Regulation in Gastric Cancer: Mechanisms, Synergies With Immunotherapy, and Future Directions

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Abstract

This review examines recent advances in the use of probiotics combined with immune modulation for the prevention and treatment of gastric cancer. It highlights the interactions between gastrointestinal probiotics, including Lactobacillus, and Helicobacter pylori infection, emphasizing their roles in gastric cancer initiation and progression. The article evaluates how probiotics exert anticancer effects by restoring intestinal microecological balance, enhancing mucosal immunity, and suppressing *H. pylori*. It also discusses preliminary findings on Lactobacillus in colorectal cancer and their potential relevance to gastric cancer research. Finally, the clinical potential of combining probiotics with immunotherapy for gastric cancer is assessed, and future research directions in this rapidly evolving field are proposed.

Keywords: probiotics; gastric cancer; immune regulation; *Helicobacter pylori*; *Lactobacillus*; gastrointestinal microecology

1. Introduction

Gastric cancer continues to be a significant global health challenge, with particularly high incidence and mortality in regions such as East Asia [1]. Its development involves a complex interplay of genetic, environmental, and microbial factors. *Helicobacter pylori* infection is the most well-established risk factor, as chronic infection can lead to gastric inflammation, atrophic gastritis, and eventually cancer [2,3]. The relationship between gastric cancer and gut microbiota has attracted increasing attention, given that microbial imbalance—dysbiosis—is implicated in various gastrointestinal disorders, including gastric cancer [4,5]. Probiotics, defined as live microorganisms that confer health benefits, may help modulate gut microbiota and enhance host immunity, offering a promising complementary strategy for gastric cancer prevention and treatment [6,7].

Recent studies have shed light on how probiotics influence the gut microbiome and immune responses, demonstrating their capacity to restore microbial balance in dysbiotic conditions. Probiotics such as *Lactobacillus* and *Bifidobacterium* exhibit anti-inflammatory properties, strengthen the gut barrier, and promote the production of short-chain fatty acids, which are protective against colorectal and gastric cancers [8,9,10]. Combining probiotics with *H. pylori* eradication therapy may also improve treatment success and reduce recurrence rates [11,12,13]. The dual benefits of probiotics for gut health and their potential to mitigate side effects of conventional cancer treatments [14] underscore their value in comprehensive gastric cancer management.

Beyond direct effects on gut microbiota, emerging evidence suggests that the gut-brain axis may also influence cancer risk and treatment outcomes [15]. Communication between gut microbiota and the central nervous system can modulate immune responses and stress pathways, which are relevant to cancer progression and patient quality of life [16]. Thus, probiotics may offer dual advantages by improving both gastrointestinal and psychological well-being, which is particularly important for patients undergoing cancer treatment.

This review systematically evaluates the role of probiotics in preventing and treating gastric cancer, with a focus on their impact on gut microbiota composition, immune modulation, and overall patient outcomes. By synthesizing current preclinical and early clinical findings, it aims to clarify potential pathways through which probiotics might be integrated into gastric cancer prevention and treatment strategies, potentially improving clinical results and patient quality of life. Given the rising incidence of gastric cancer and the need for effective preventive measures, exploring probiotics as a complementary approach presents promising opportunities for future research and clinical application. However, it is crucial to interpret the available data cautiously, as robust clinical validation from large-scale trials is still needed (The literature search strategy is detailed in the **Supplementary Material**).

2. Main

2.1 The Association Mechanism Between Gastric Cancer and Gastrointestinal Microecological Imbalance

2.1.1 Molecular Pathways of Gastric Cancer Induced by *Helicobacter pylori* Infection

Helicobacter pylori is widely recognized for its role in gastric cancer development. Its virulence factors, particularly CagA and VacA, are central to oncogenic signaling. The CagA protein enters gastric epithelial cells via the type IV secretion system and, upon phosphorylation, activates pathways such as Phosphatidylinositol 3-kinase/Protein kinase B (PI3K/Akt) and Mitogen-activated protein kinase (MAPK). These pathways promote cell proliferation, survival, and migration, contributing to gastric carcinogenesis [17,18]. VacA, another key virulence factor, induces vacuolation in gastric epithelial cells and modulates immune responses, leading to chronic inflammation and further DNA damage. The chronic inflammatory state triggered by *H. pylori* infection involves immune cell infiltration and the release of pro-inflammatory cytokines, creating a microenvironment favorable to malignant transformation [19,20]. The interaction between these virulence factors and host cellular signaling pathways illustrates the complex mechanisms through which *H. pylori* promotes gastric cancer.

Additionally, *H. pylori* infection can induce epigenetic changes, including DNA methylation alterations that silence tumor suppressor genes and activate oncogenes, further driving cancer progression [21,22]. The combined effects of chronic inflammation, oxidative stress, and epigenetic modifications create a conducive environment for gastric cancer development.

Dysbiosis resulting from *H. pylori* infection also plays a critical role in gastric carcinogenesis. *H. pylori* alters gastric microbiota composition, reducing beneficial microbes and increasing pathogenic ones. This imbalance can exacerbate inflammation and promote precancerous lesions [17,23]. Moreover, the altered microbial environment can affect host immune responses and metabolic pathways, contributing to carcinogenesis. Recent studies suggest that specific microbial signatures associated with *H. pylori* infection may serve as biomarkers for gastric cancer risk, highlighting the potential for microbiome-based interventions in cancer prevention [23,24]. Understanding the interactions between *H. pylori*, host immunity, and microbial communities is essential for developing targeted strategies to reduce gastric cancer risk.

In summary, *H. pylori* induces gastric cancer through multiple molecular pathways, including direct oncogenic signaling via virulence factors, chronic inflammation leading to DNA damage, and dysbiosis contributing to carcinogenesis. Continued research into these mechanisms is vital for identifying therapeutic targets and preventive measures against *H. pylori*-induced gastric cancer. Integrating microbial and host factors may lead to innovative approaches for reducing the burden of this malignancy.

2.1.2 The Correlation Between Gut Microbiota Composition and Gastric Cancer Risk

The relationship between gut microbiota composition and gastric cancer risk has received considerable attention in recent years, especially with advances in molecular biology and sequencing technologies that reveal the complex dynamics of gastrointestinal microbial communities. Meta-analyses have shown distinct differences in gut microbiota profiles between gastric cancer patients and healthy individuals, indicating that dysbiosis may play a pivotal role in carcinogenesis. For example, the abundance of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* is often reduced in gastric cancer patients, whereas pathogenic bacteria like *Helicobacter pylori* are frequently overrepresented [25].

Furthermore, certain microbial communities modulate inflammatory responses and produce metabolites that influence tumor development. Microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids have been implicated in gastric cancer, underscoring the importance of microbial metabolic activity in the disease's etiology [26].

A dose-response relationship between specific bacterial species and gastric cancer risk has also been observed. A two-sample Mendelian randomization study identified protective associations with genera such as *Clostridium sensu stricto* and *Actinomycetales*, while an increase in taxa like *Roseburia* was linked to higher gastric cancer risk [27]. This suggests that the relative abundance of certain microbial populations significantly influences cancer susceptibility. The mechanisms through which gut microbiota affect gastric cancer risk are multifaceted, involving immune modulation, inflammation, and the production of carcinogenic metabolites. These interactions highlight the potential of gut microbiota as biomarkers for risk assessment and as targets for therapeutic intervention [28].

In addition to direct microbial effects, metabolic products of gut microbiota play a crucial role in gastric cancer pathogenesis. SCFAs, for instance, exert anti-inflammatory effects and support epithelial health, whereas dysbiosis can lead to harmful metabolites that promote carcinogenesis [29]. The relationship between gut microbiota, their metabolites, and the host immune response is complex and requires further investigation. Understanding these interactions may lead to novel strategies for gastric cancer prevention and treatment, including dietary modifications and probiotic interventions aimed at restoring a healthy gut microbiota balance [30].

Overall, compelling evidence supports the correlation between gut microbiota composition and gastric cancer risk, emphasizing the need for continued research. Further elucidation of these mechanisms could identify new biomarkers for early detection and enable microbiota-targeted therapies that enhance existing treatments. Integrating microbiome research into clinical practice may im-

prove our understanding of gastric cancer and lead to more personalized prevention and therapy.

2.2 Mechanisms of Probiotics in Anti-Gastric Cancer

2.2.1 Inhibition of *Helicobacter pylori* by Probiotics

Probiotics have gained attention for their ability to inhibit *Helicobacter pylori*, a bacterium linked to chronic gastritis and gastric cancer. One key mechanism is competitive inhibition, where probiotic strains, particularly *Lactobacillus*, adhere to the gastric mucosa, preventing *H. pylori* colonization. For example, *Lactobacillus reuteri* can inhibit *H. pylori* adhesion to porcine gastric mucin, reducing its ability to attach to the gastric lining [31]. This competitive exclusion not only limits *H. pylori* colonization but also modulates the host immune response, reducing inflammation and associated gastric damage [32].

Probiotics also produce antimicrobial substances such as bacteriocins and organic acids that directly target *H. pylori*. Bacteriocins are antimicrobial peptides that disrupt bacterial cell membranes, leading to cell death. Strains like *Lactobacillus casei* and *Lactobacillus rhamnosus* produce bacteriocins that inhibit *H. pylori* growth *in vitro* [33]. Organic acids, including lactic acid, lower the gastric pH, creating an unfavorable environment for *H. pylori* survival [34]. This combination of competitive inhibition and antimicrobial production illustrates the multi-faceted approach of probiotics against *H. pylori*.

Moreover, probiotics enhance gastric mucosal barrier function, which is crucial for protecting against *H. pylori*-induced damage. Probiotics stimulate mucus production and increase the expression of tight junction proteins, maintaining epithelial barrier integrity [35] (Fig. 1). *Lactobacillus reuteri*, for instance, upregulates mucin genes, thickening the mucus layer and providing a physical barrier against *H. pylori* [36]. Probiotics also modulate immune responses by enhancing immunoglobulin A (IgA) secretion and other protective factors, strengthening mucosal defense [37].

These mechanisms translate into clinical benefits. A randomized controlled trial demonstrated that adding a specific four-probiotic mixture (*Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium lactis*, and *Saccharomyces boulardii*) to standard eradication therapy significantly improved outcomes, yielding a higher eradication rate (92.0% vs 86.8%) and substantially fewer side effects (17.0% vs 50.7%) compared to placebo [38].

In summary, probiotics inhibit *H. pylori* through competitive exclusion, antimicrobial production, and enhancement of mucosal barrier function. These mechanisms suppress *H. pylori* directly and support overall gastrointestinal health. As antibiotic resistance challenges conventional treatments, integrating probiotics into eradication protocols offers a promising approach to improve outcomes and reduce side effects. Future research should identify the most effective probiotic strains and clarify their mechanisms to optimize clinical use.

2.2.2 Specific Counteraction of *H. pylori* Virulence Factors

Building upon general inhibitory mechanisms, recent research has elucidated precise ways probiotics counteract specific *H. pylori* virulence factors central to gastric carcinogenesis.

CagA Counteraction: The CagA oncoprotein, translocated via the type IV secretion system (T4SS), represents a primary carcinogenic driver. Probiotics impede CagA pathogenicity through multiple mechanisms. Lactobacillus gasseri and *L. reuteri* competitively occupy integrin receptors ($\alpha5\beta1$) and lipid raft microdomains that serve as CagA injection portals, reducing CagA translocation by 45–60% in co-culture models [39]. Additionally, bacteriocins produced by *L. casei* (caseicin A) downregulate cagA gene expression by interfering with *H. pylori* quorum-sensing systems, suppressing CagA protein production at the transcriptional level [40]. Post-translocation, probiotic-derived butyrate inhibits SRC-mediated CagA phosphorylation, mitigating downstream PI3K/Akt and MAPK oncogenic signaling [41].

VacA Neutralization: VacA induces vacuolation and apoptosis through pore formation in epithelial cells. Probiotics counteract VacA through pH modulation and barrier enhancement. Lactic acid production lowers gastric pH to $<$4.5, causing VacA oligomer disassembly and preventing functional pore formation [42]. Concurrently, probiotics upregulate MUC5AC and MUC6 expression, creating a denser mucus layer that limits VacA diffusion to epithelial surfaces. *L. rhamnosus* GG has been shown to reduce VacA-induced vacuolation by 70% in gastric epithelial cell lines through these combined effects [43].

BabA and Adhesion Inhibition: BabA (blood group antigen-binding adhesin) mediates *H. pylori* attachment to Lewis b antigens. Probiotic SCFAs, particularly propionate, suppress babA gene expression by 35–40% [44]. Simultaneously, competitive exclusion by Lactobacillus species physically blocks BabA binding sites, reducing *H. pylori* colonization density.

Protease and Urease Inhibition: *H. pylori* secretes proteases that degrade gastric mucus and urease that neutralizes gastric acid. Probiotic strains produce protease inhibitors and directly inhibit urease activity by 25–30%, as demonstrated by Bifidobacterium bifidum [45]. This multi-targeted approach underscores the therapeutic potential of precisely selected probiotic strains in mitigating *H. pylori*-driven carcinogenesis.

2.2.3 Mechanisms of Probiotics in Modulating the Immune System Against Tumors

Probiotics show promise as adjuncts in cancer therapy through their immunomodulatory effects. One key mechanism is the activation of dendritic cells (DCs) and regulatory T cells (Tregs) (Fig. 1). Probiotics enhance DC maturation and function, improving antigen presentation and immune response initiation. Strains such as *Lactobacillus*

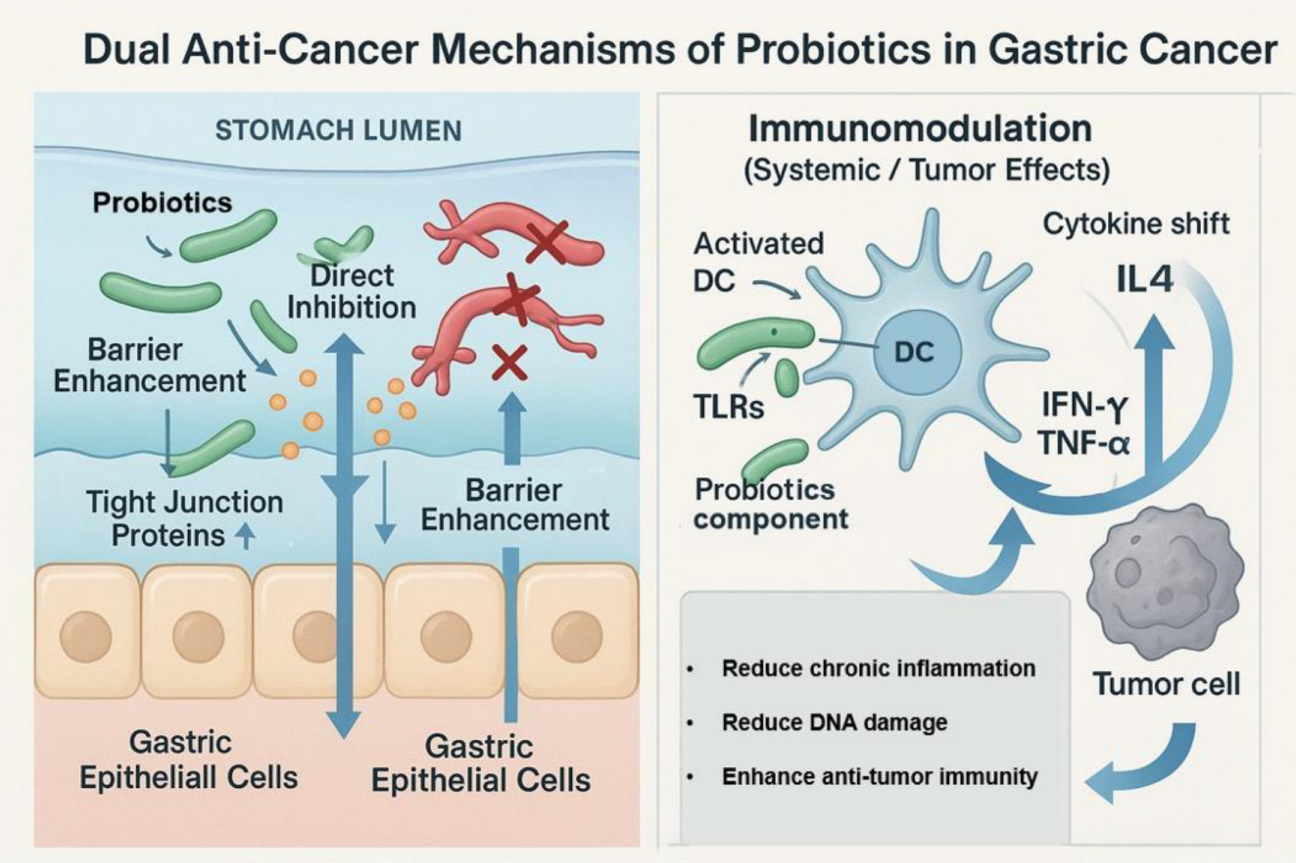

Fig. 1. Dual anti-cancer mechanism of probiotics in gastric cancer. DC, dendritic cell; TLR, toll-like receptor; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; IL-4, interleukin 4.

and *Bifidobacterium* upregulate co-stimulatory molecules on DCs, promoting naïve T cell activation and a stronger anti-tumor response [46,47]. Probiotics also modulate Treg populations, shifting the immune balance from suppression to activation, enhancing the ability to target tumor cells.

Probiotics also engage Toll-like receptor (TLR) signaling on immune cells, triggering the production of pro-inflammatory cytokines and activating macrophages and T cells. This interaction boosts innate immunity and shapes adaptive immune responses. For example, probiotic components can enhance interleukin-12 (IL-12) and interferon-gamma (IFN-γ) production, promoting Th1 responses critical for anti-tumor immunity [48,49]. Additionally, probiotics modulate gut microbiota composition, leading to metabolite production that further enhances immune responses.

Probiotics influence the Th1/Th2 balance and cytokine network, shifting immunity toward a Th1-dominant profile characterized by increased IFN-γ and tumor necrosis factor-alpha (TNF-α), while reducing Th2-associated cytokines like IL-4. This shift is important because Th1 responses are associated with anti-tumor activity, whereas Th2 responses may promote tumor growth. Specific probiotic strains enhance Th1 cytokines and inhibit Th2 cytokines, creating a favorable immune environment for tumor eradication [50,51].

In conclusion, probiotics modulate the immune system through DC and Treg activation, TLR signaling, and Th1/Th2 balance regulation. These actions collectively enhance anti-tumor immunity, supporting the use of probiotics in cancer prevention and treatment. Further research is needed to identify the most effective strains and dosages for different cancer contexts.

2.3 Probiotic Strains From Traditional Fermented Foods: Insights From "Jiangshui" With Relevance to Gastrointestinal Cancers

The complex interplay between the host immune system and the gut microbiota is increasingly recognized as a pivotal factor in the development and progression of various malignancies, including gastric cancer (GC), colorectal cancer (CRC), and lung cancer. Probiotics, defined as live microorganisms that confer a health benefit, represent a promising adjunctive strategy in oncology by restoring microbial homeostasis, modulating chronic inflammation, and influencing metabolic pathways. A particularly rich source of such beneficial bacteria is "Jiangshui", a traditional fermented vegetable broth popular in Northwest China, char-

acterized by its abundance of Lactobacillus species. Recent research has begun to elucidate the specific mechanisms of "Jiangshui"-derived strains, suggesting significant therapeutic potential across these three cancer types. This section highlights specific mechanisms of "Jiangshui"-derived strains relevant to gastrointestinal health and carcinogenesis, acknowledging that potential clinical evidence in gastric cancer is still emerging.

Targeting Gastrointestinal Cancers Through Metabolic and Inflammatory Modulation

The established links between chronic inflammation, gut dysbiosis, and the oncogenesis of CRC and GC provide a strong rationale for probiotic intervention. Strains extracted from "Jiangshui" demonstrate potent capabilities in modulating key metabolic pathways relevant to gut health. For instance, one such probiotic was shown to target bile acid metabolism to alleviate Ulcerative Colitis (UC), a major risk factor for CRC [52]. By effectively reducing pro-inflammatory conjugated bile acids, the probiotic directly addresses a critical mechanism of mucosal damage and carcinogenesis.

Jiangshui-derived Limosilactobacillus fermentum strains exhibit robust bile salt hydrolase (BSH) enzymatic activity (>500 U/mg protein), which deconjugates conjugated bile acids (glycocholate, taurocholate) into free bile acids. This enzymatic conversion reduces the cytotoxicity of conjugated bile acids on gastric and colonic epithelia by 40–50% [53] (Fig. 2). Additionally, these strains possess 7α-dehydroxylation capabilities, converting primary bile acids (cholic acid, chenodeoxycholic acid) to less toxic secondary bile acids (deoxycholic acid, lithocholic acid), thereby altering the bile acid pool composition [54].

The metabolic shift in bile acids modulates critical signaling pathways. By reducing conjugated bile acids, probiotics decrease farnesoid X receptor (FXR) antagonism in intestinal epithelial cells, restoring FXR-mediated suppression of NF-κB signaling and reducing pro-inflammatory cytokine production. Concurrently, increased secondary bile acids activate TGR5 receptors, enhancing IL-10 production and regulatory T cell function, creating an anti-inflammatory environment less permissive to cancer progression [55]. In clinical pilot studies, Jiangshui probiotic supplementation (10^9 CFU/day for 8 weeks) reduced fecal conjugated bile acids by 35–40% in UC patients, correlating with decreased IL-6 ($p < 0.01$) and TNF-α ($p < 0.001$) levels. For gastric cancer prevention, this mechanism is particularly relevant in the gastric cardia, where bile acid reflux-induced epithelial damage represents a significant risk factor [56].

Beyond bile acid modification, other "Jiangshui" strains, such as Limosilactobacillus fermentum JL-3, exhibit systemic anti-inflammatory benefits by degrading uric acid to meliorate hyperuricemia [57] (Fig. 2). The resulting decrease in systemic inflammation is a crucial factor in creating a host environment less susceptible to cancer progression. Furthermore, the detoxification properties demonstrated by the *L. fermentum* GR-3 strain, which reduces the accumulation of the heavy metal arsenic [58], highlight an additional protective mechanism against exposure to a known GC carcinogen. These combined effects—bile acid manipulation, inflammation control, and detoxification—underscore the potential of "Jiangshui" strains in the supportive care for gastrointestinal malignancies.

It is noted that some research on "Jiangshui" probiotics has explored effects on respiratory health via the gut-lung axis [59]. While this illustrates the broad systemic immunomodulatory potential of probiotics, the primary focus of this review remains on gastrointestinal cancers. The gut-lung axis serves as an example of remote organ effects but will not be discussed in detail here.

In summary, probiotics strains from traditional sources "Jiangshui", particularly those within the *Limosilactobacillus* genus, possess diverse properties that make them highly relevant candidates for adjunct therapy in gastrointestinal cancer. Their demonstrated ability to control key oncogenic drivers, including chronic inflammation, pathogenic bile acid profiles, and toxic accumulation, provides a robust mechanistic foundation. Further clinical investigation is warranted to transition these promising *in vitro* and animal-model findings into established clinical protocols for cancer prevention, mitigation of treatment side effects, and improved overall patient outcomes.

2.4 Synergistic Effects of Probiotics Combined With Immunotherapy in Gastric Cancer

2.4.1 Mechanisms by Which Probiotics Enhance the Efficacy of Immune Checkpoint Inhibitors

Combining probiotics with immune checkpoint inhibitors (ICIs) has emerged as a promising strategy to improve cancer treatment outcomes. Preclinical evidence indicates that probiotics can enhance response rates to Programmed cell death protein 1/Programmed death-ligand 1 (PD-1/PD-L1) inhibitors. Specific probiotic strains modulate the gut microbiota, which in turn influences systemic immune responses. The gut microbiome shapes T cell responses, and its alteration can enhance T cell infiltration and activation in the tumor microenvironment—key factors for ICI success. Probiotics increase beneficial microbes that produce short-chain fatty acids (SCFAs), promoting T cell differentiation and anti-tumor immunity [60]. Additionally, probiotics may reduce immune-related adverse events (irAEs) associated with ICIs by restoring gut microbiota balance and mitigating gastrointestinal toxicities, enabling sustained treatment and better patient outcomes [61].

Probiotics enhance T cell activation and infiltration by modulating cytokine profiles and improving antigen presentation. They stimulate dendritic cells and macrophages, increasing pro-inflammatory cytokines such as IL-12 and TNF-α, which are crucial for T cell activation [62]. Cer-

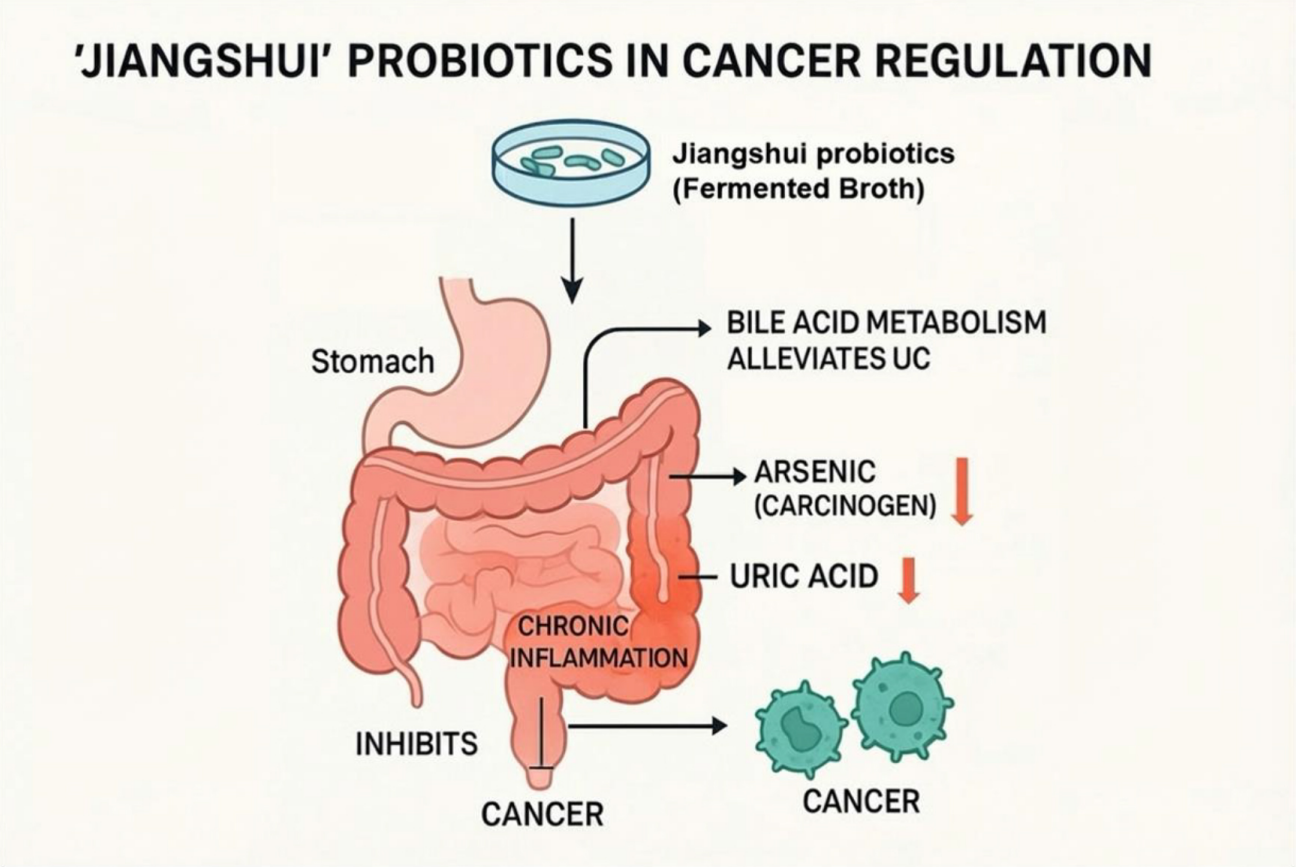

Fig. 2. 'Jiangshui' probiotics in cancer regulation. UC, Ulcerative Colitis.

tain probiotic strains also enhance major histocompatibility complex (MHC) expression on antigen-presenting cells, improving T cell recognition of tumor antigens [63]. This interaction boosts T cell activation and promotes memory T cell development, supporting long-term anti-tumor immunity. The synergy between probiotics and ICIs underscores the importance of the gut microbiome in cancer immunotherapy, though clinical validation is ongoing.

Probiotics may also alleviate immune-related adverse effects of ICIs, which result from an overactive immune response. By maintaining intestinal barrier integrity and reducing systemic inflammation, probiotics can lower the incidence and severity of irAEs [64]. Specific strains are associated with decreased inflammatory markers and improved gut health, mitigating gastrointestinal toxicities linked to ICIs [65]. This dual role—enhancing anti-tumor immunity while reducing adverse effects—positions probiotics as valuable adjuncts in cancer therapy, particularly for patients receiving ICIs. However, results across studies are variable, and strain-specific effects are critical.

In summary, probiotics enhance ICI efficacy through gut microbiome modulation, T cell activation, and reduction of immune-related adverse events. These preclinical and early clinical insights support the investigation of probiotics as a complementary strategy in cancer immunotherapy, warranting further robust clinical trials to optimize their combination with ICIs and identify responsive patient populations.

2.4.2 Gastric Cancer-Specific Mechanisms of ICI Enhancement

While general immunomodulatory effects are established, gastric cancer exhibits unique molecular characteristics that probiotic augmentation specifically targets. Recent translational studies provide mechanistic clarity for this malignancy.

MHC Class I Upregulation and Tumor Visibility: Gastric cancers frequently downregulate MHC class I expression as an immune evasion mechanism. Specific probiotic strains (*L. rhamnosus* GG, *B. animalis subsp. lactis* BB-12) increase IFN-γ production by 2.5–3 fold, which subsequently upregulates Major histocompatibility complex I (MHC-I) and PD-L1 expression on gastric tumor cells [66]. This seemingly paradoxical effect increases tumor antigen visibility to $CD8^+$ T cells while simultaneously sensitizing them to PD-1/PD-L1 blockade, a critical requirement for ICI efficacy in MHC-I-low tumors.

CXC Chemokine Receptor 3, C-X-C motif chemokine 10 (CXCR3/CXCL10) Axis and T-Cell Trafficking: SCFAs, particularly propionate produced by probiotic Bifidobacterium strains, induce gastric epithelial cells to secrete

CXCL10 at concentrations of 150–200 pg/mL [67]. This chemokine gradient facilitates homing of $CXCR3^+$ effector T cells to the gastric tumor microenvironment. Analysis of the CheckMate-649 trial revealed that gastric cancer patients with high baseline Bifidobacterium abundance (>8% of gut microbiota) showed 3-fold higher intratumoral CXCL10 levels and significantly improved objective response rates to nivolumab (58% vs 32%, $p = 0.003$) [68].

Treg/Teffector Rebalancing: The gastric tumor microenvironment is characterized by high Forkhead box P3 ($FOXP3^+$) regulatory T cell infiltration. Probiotic administration reduces Treg frequencies from 25–30% to 12–15% of tumor-infiltrating lymphocytes while increasing the Cytotoxic T lymphocytes/ Regulatory T Cells ($CD8^+$/Treg) ratio from 1.2 to 3.8, thereby enhancing ICI-mediated cytotoxicity [69].

Metabolic Reprogramming of T Cells: L. reuteri produces indole-3-aldehyde, a tryptophan metabolite that competes with tumor-derived kynurenine for aryl hydrocarbon receptor (AhR) binding, preventing AhR-mediated T cell exhaustion [70]. This metabolic intervention maintains T cell stemness and proliferative capacity, synergizing with PD-1 blockade to sustain anti-tumor responses.

In summary, probiotics enhance ICI efficacy through gut microbiome modulation, T cell activation, MHC upregulation, enhanced trafficking, and reduction of immune-related adverse events. These gastric cancer-specific insights support the use of probiotics as a complementary strategy in cancer immunotherapy, warranting further clinical investigation to optimize their combination with ICIs.

2.4.3 Probiotics Combined With Traditional Gastric Cancer Treatment Strategies

The integration of probiotics with conventional gastric cancer treatments such as chemotherapy and radiotherapy has shown potential in reducing treatment-related side effects. Clinical studies indicate that probiotics can alleviate gastrointestinal toxicity commonly associated with chemotherapy. For example, strains like *Lactobacillus* and *Bifidobacterium* reduce the incidence of chemotherapy-induced diarrhea and mucositis, improving treatment tolerance [71]. A multicenter randomized controlled trial found that patients receiving neoadjuvant chemotherapy supplemented with probiotics had fewer postoperative infections and faster recovery of gastrointestinal function compared to those without probiotics [72]. This suggests that probiotics enhance gut barrier function and modulate inflammatory responses, which are often compromised during chemotherapy.

Probiotics also improve nutritional status and quality of life in gastric cancer patients undergoing radiotherapy, which can cause weight loss and nutritional deficiencies. Probiotic administration has been shown to improve serum albumin and prealbumin levels, key markers of nutritional status [73]. Patients receiving probiotics during radiotherapy reported better quality of life scores, indicating improved well-being and functional status. These findings support the inclusion of probiotics in treatment regimens to alleviate side effects and maintain nutritional health.

Postoperative recovery is another area where probiotics demonstrate benefits. After radical gastrectomy, probiotics can accelerate the restoration of gastrointestinal function, as seen in shorter times to first flatus and bowel movement [74]. Probiotics modulate gut microbiota, enhancing microbial diversity and restoring a healthy gut environment. They may also support immune reconstitution, reducing postoperative infections and inflammation [75].

Overall, combining probiotics with traditional gastric cancer treatments offers a promising approach to improve patient outcomes by reducing toxicity, enhancing nutrition, and supporting recovery. Future research should identify the most effective strains and dosages for these applications.

2.5 Challenges and Solutions in the Clinical Application of Probiotics

2.5.1 Strain-Specificity and Personalized Treatment Strategies

The efficacy of probiotics in gastric cancer prevention and treatment is often strain-specific, emphasizing the need for careful strain selection. Different strains of *Lactobacillus* and *Bifidobacterium* exhibit distinct mechanisms, such as inhibiting *Helicobacter pylori* or modulating immune responses. *Lactobacillus rhamnosus*, for example, enhances immunity while reducing inflammation, contributing to its protective effects against gastric cancer [76]. Identifying strains that modulate the gut microbiota and enhance anti-tumor immunity is crucial for developing personalized treatments. This approach aligns with precision medicine, where regimens are tailored based on individual microbiome profiles, genetic factors, and cancer type [77].

Personalized probiotic formulations can be designed based on patient-specific microbiota profiles. Gut microbiota composition influences probiotic response, and patients with different microbial signatures may benefit from tailored strains or combinations. This personalized strategy improves efficacy and minimizes adverse effects. Genomic and metagenomic techniques can analyze patient microbiota, guiding the development of customized probiotic therapies [78]. Integrating genomic data with clinical outcomes may identify biomarkers predictive of probiotic response, enabling more individualized interventions [79].

Genomic insights also support the development of precision microbiome interventions. Bioengineering can create probiotic strains with enhanced anti-cancer properties or improved colonization in the gastrointestinal tract. Synthetic biology approaches may yield probiotics that deliver therapeutics directly to tumor sites, offering a promising frontier in cancer treatment [80]. Such customization could improve efficacy, reduce resistance, and enhance patient outcomes.

Translating personalized probiotic concepts into clinical practice requires a systematic framework. We propose a four-step precision development pipeline specifically for gastric cancer management.

Precision probiotic development for gastric cancer envisions a streamlined framework integrating multidimensional microbiome profiling and host factors to guide personalized interventions. The pipeline begins with baseline assessment via 16S rRNA sequencing and shotgun metagenomics to identify predictive biomarkers—such as low Lactobacillus (<5%), high Fusobacterium (>3%), reduced SCFA-producing taxa, and elevated inflammatory potential—and functional capacities like BSH enzyme activity [81]. Host genetics (IL-1β-511, TNF-α-308, TLR4 polymorphisms) further stratify patients, with high-risk genotypes potentially requiring higher doses (10^{10} vs 10^{9} CFU) and anti-inflammatory strains tailored to treatment phase (L. reuteri DSM 17938 for *H. pylori* eradication; *B. animalis subsp. lactis* BB-12 post-gastrectomy) [82]. Algorithm-driven selection then matches formulations to patient profiles: multi-strain cocktails ($\geq$5 strains) for dysbiosis index >2.0, butyrate-producers (*L. plantarum* WCFS1) for SCFA deficiency, and IL-10-inducing strains (*L. rhamnosus* GG) for high inflammation. Adaptive monitoring via stool qPCR (weeks 2, 4, 8) ensures colonization $>10^{6}$ CFU/g, with inflammatory markers guiding dose optimization. Future clinical trials should stratify gastric cancer patients by microbiota signatures to validate this personalized approach, evaluating safety, colonization kinetics, immune modulation, and quality of life as key outcomes (Fig. 3).

In conclusion, strain-specificity and personalized treatment strategies represent significant advances in probiotic therapy for gastric cancer. Tailoring interventions based on individual microbiota profiles can optimize outcomes and improve the effectiveness of probiotic treatments. Future research should further explore the relationships between probiotics, gut microbiota, and host immunity to develop more personalized gastric cancer management approaches.

2.5.2 Optimization of Dosage Regimens and Formulation Improvements

Optimizing dosage regimens and formulations is essential for improving probiotic efficacy in gastric cancer prevention and treatment. A key challenge is ensuring probiotic survival in the harsh gastric environment. Recent advances include encapsulation techniques such as microencapsulation and nanoencapsulation, which protect probiotics from gastric acid and enable targeted release in the intestines. Probiotics encapsulated in materials like alginate or chitosan show higher survival rates in acidic conditions, enhancing their therapeutic potential [83]. Improved delivery systems can also optimize probiotic pharmacokinetics, supporting effective gut colonization.

Targeted delivery systems, including microcapsules and nanocarriers, represent a promising direction in probiotic research. Microencapsulation protects probiotics from environmental stressors and allows controlled release, ensuring viable delivery to the intestines. Nanocarriers such as liposomes and polymeric nanoparticles can encapsulate probiotics and facilitate transport across biological barriers, improving solubility and bioavailability [84]. These systems may enhance probiotic retention and bioactivity in the gut, supporting anti-cancer effects.

Synergistic effects between probiotics and prebiotics are also under investigation. Prebiotics serve as food for probiotics, promoting their growth and activity. Identifying optimal probiotic-prebiotic combinations and ratios is critical for enhancing gut health and immune responses (Fig. 3). For example, combining inulin with specific *Lactobacillus* strains has shown promise in improving gut health and reducing inflammation, which is relevant to gastric cancer [85]. Research on synbiotic formulations may lead to enhanced protective effects against gastric cancer.

2.5.2.1 Microencapsulation Technologies. Alginate-Based Systems: Ionotropic gelation using calcium chloride creates 200–500 µm beads achieving 85–90% survival at pH 2.0 for 2 hours. L. acidophilus encapsulated in 2% alginate with 0.5% chitosan coating demonstrates 10^{7} CFU/mL recovery versus 10^{3} CFU/mL for free cells [86].

Protein-Polysaccharide Complexes: Whey protein isolate-chitosan coacervates provide pH-responsive protection, remaining compact at gastric pH 1.5–3.5, then swelling and releasing contents at intestinal pH >6.0, achieving 95% viability [87].

Spray-Drying with Protective Carriers: Skim milk powder (20% w/v) + trehalose (10% w/v) as wall materials yields dried powders with 80% viability and 12-month stability at 4 °C, suitable for resource-limited settings [88].

2.5.2.2 Nanoencapsulation for Enhanced Delivery. Liposomal Systems: Phospholipid bilayer vesicles (100–200 nm) encapsulating probiotics show 92% survival in simulated gastric fluid. Soy lecithin liposomes facilitate targeted release triggered by intestinal bile salts, improving mucosal adhesion by 3-fold [89].

Polymeric Nanoparticles: PLGA (poly-lactic-co-glycolic acid) nanoparticles (150 nm diameter) provide pH-dependent degradation, releasing probiotics specifically in the duodenum with 88% survival and enhanced mucoadhesion via chitosan coating [90] (Fig. 3).

In summary, optimizing probiotic dosage and formulation involves improving acid survival, developing targeted delivery systems, and exploring probiotic-prebiotic synergies. These advancements hold great potential for enhancing probiotic efficacy in gastric cancer prevention and treatment, contributing to better clinical outcomes. Future research should refine these approaches and establish standardized protocols for clinical use.

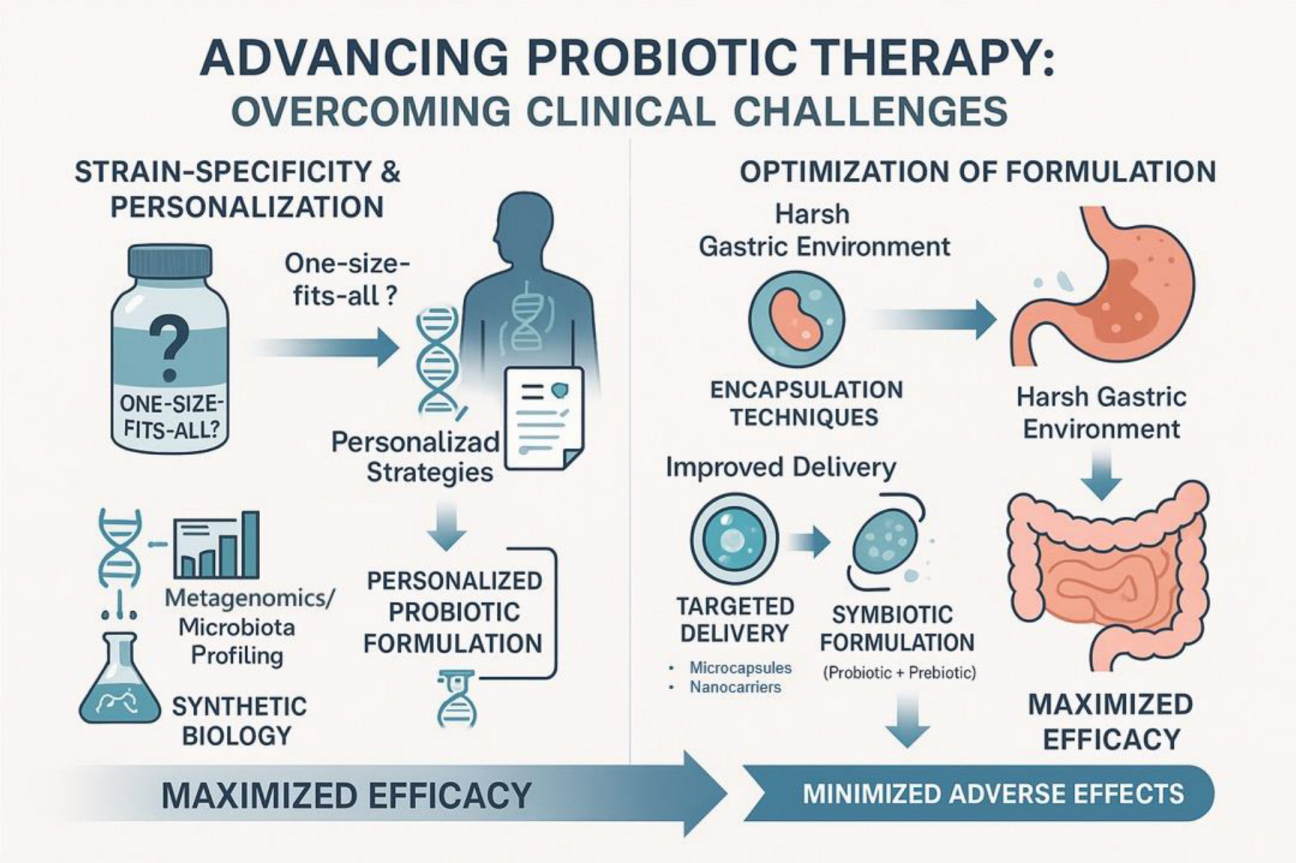

Fig. 3. Challenges and solutions of probiotics in clinical applications.

3. Conclusion

Research on probiotics, particularly water-soluble forms, in gastric cancer prevention and treatment reveals a promising multi-target and multi-pathway approach. Insights from colorectal cancer studies inform potential strategies for gastric cancer, supporting the exploratory development of novel therapies that might incorporate probiotics into comprehensive cancer management.

As microbiome research and oncology converge, a balanced perspective is needed to interpret diverse findings and methodologies. While probiotics show potential in modulating gut microbiota and immune responses, individual variability necessitates a deeper understanding. Future studies should prioritize high-quality clinical trials evaluating specific probiotic strains in diverse populations. These trials should clarify the mechanisms of probiotic action, enhancing their role in gastric cancer prevention and treatment.

Multi-omics technologies and synthetic biology offer exciting opportunities for personalized probiotic therapies. Genomic, transcriptomic, proteomic, and metabolomic data can identify biomarkers predicting individual responses to probiotics, enabling tailored treatments that maximize efficacy and minimize adverse effects.

The future of gastric cancer prevention, diagnosis, and treatment may be transformed as we unravel the gut microbiome's interactions with host physiology. Probiotics as adjuncts to immunotherapy are particularly promising, opening new avenues for improving patient outcomes. Realizing this potential requires collaboration among researchers, clinicians, and industry partners to translate scientific discoveries into clinical practice.

In conclusion, while the field of probiotics in gastric cancer is still evolving, this review highlights the importance of a comprehensive and integrative approach. Balancing diverse research perspectives will be essential for harnessing the full potential of probiotics. Rigorous scientific inquiry, interdisciplinary collaboration, and patient-centered research will shape the future of gastric cancer prevention and treatment, offering the promise of improved outcomes and renewed understanding of cancer therapy in the context of gastrointestinal health.

Author Contributions

NW and FXS contributed to the conceptualization of the work, collected, organized, and analyzed literature materials, and performed the original draft preparation. HC was responsible for references collection and reviewing. XKL provided conceptualization, supervision, and also re-

viewed and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBL48167.

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