Probiotics and Antimicrobial Proteins
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REVIEW

Potential of Synbiotics and Probiotics as Chemopreventive Agent

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Abstract
Cancer remains a global problem, with millions of new cases diagnosed yearly and countless lives lost. The financial burden of cancer therapy, along with worries about the long-term safety of existing medicines, necessitates the investigation of alternative approaches to cancer prevention. Probiotics generate chemopreventive compounds such as bacteriocins, short-chain fatty acids (SCFA), and extracellular polymeric substances (EPS), which have demonstrated the ability to impede cancer cell proliferation, induce apoptosis, and bolster the expression of pro-apoptotic genes. On the other hand, prebiotics, classified as non-digestible food ingredients, promote the proliferation of probiotics within the colon, thereby ensuring sustained functionality of the gut microbiota. Consequently, the synergistic effect of combining prebiotics with probiotics, known as the synbiotic effect, in dietary interventions holds promise for potentially mitigating cancer risk and augmenting preventive measures. The utilization of gut microbiota in cancer treatment has shown promise in alleviating adverse health effects. This review explored the potential and the role of probiotics and synbiotics in enhancing health and contributing to cancer prevention efforts. In this review, the applications of functional probiotics and synbiotics, the mechanisms of action of probiotics in cancer, and the relationship of probiotics with various drugs were discussed, shedding light on the potential of probiotics and synbiotics to alleviate the burdens of cancer treatment.

Keywords Cancer · Functional foods · Gut health · Microbiome

Introduction

Cancer caused by unregulated cell proliferation that leads to benign or malignant tumor growth is currently one of the top causes of death globally. About 19.3 million new cancer cases were recorded globally in 2020, leading to 10 million fatalities due to cancer's lethal malignancy trait [1]. Nowadays, oncology medications are used alongside other treatment modalities, including chemotherapy, radiation therapy, and surgery [2]. In 2017, patients paid an average of $229,295.33 for breast cancer treatment [3]. Costs for breast cancer treatment ranged from $60,637 to $134,682, almost triple the cost from stage I to IV [4]. Moreover, a study has shown that the average distance for a patient to enrol for the facility in Malaysia was 41.4 km with a minimal cost of $14.08 [5]. Aside from the exorbitant cost of cancer treatments, the long-term safety of synthetic medications in contemporary cancer treatments is debatable. According to [6], the accumulation of toxins in the body from continuously administering chemotherapy medications might cause catastrophic side effects such as dermatologic, ventricular dysfunction, and ophthalmologic. In light of this, developing low-cost chemopreventive treatments for minimal toxicity is critical.

The dietary intake and contemporary lifestyle have also increased the occurrence of methemoglobin and other disorders [7]. In fact, more than half of cancer occurrences, diabetes and cardiovascular diseases, and deaths are preventable, in which 30% of cancer is related to nutrition intake and diet [8]. Recent research has highlighted the significant impact of

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probiotics and synbiotics on health, suggesting their potential as chemopreventive agents. Functional foods such as yogurt, kefir, miso, tempeh, sauerkraut, and sourdough are known to enhance health outcomes due to their probiotic properties [9]. Extensive studies have demonstrated the role of microbes in cancer biology, including their involvement in metabolic regulation, the gut-brain axis, immune system development, and gastrointestinal carcinogenesis. Importantly, probiotics in the gut microbiota have been shown to mitigate the adverse effects of chemotherapy [10–12]. Predominant intestinal microbes such as *Lactobacillus* and *Bifidobacterium* have been documented to bind with and deactivate carcinogens at the initial stages of colon carcinogenesis [13]. *Lactobacillus plantarum* KU15149 and *Bifidobacterium pseudocatenulatum* G7 have been reported to adhere to gut immune cells, influence toll-like receptor signaling, increase pro-inflammatory cytokine levels, and modulate T cells, thereby inhibiting cancer development [14, 15].

The global market for probiotics was valued at approximately $57.8 billion in 2022, with forecasts projecting growth to reach $85.4 billion by 2027 [16]. This growth is driven by their recognized benefits in improving gut health, enhancing livestock and pet performance, reducing mortality rates, and even in applications such as edible films and coatings that enhance food safety and preservation [17]. The probiotics industry has evolved into a multi-billion-dollar sector within the human consumption market alone. Probiotics have been employed to reduce mortality rates in fish, enhance growth in piglets, improve egg production quality in poultry, fortify immune defenses in fish, and mitigate *Salmonella* contamination in chickens [18–22]. Moreover, incorporating probiotics into edible films and coatings, such as a gelatin-based coating with inulin and *Lacticaseibacillus rhamnosus* used on fresh strawberries, has notably enhanced product stability and functional properties, maintaining probiotic viability while reducing pathogen counts and preserving strawberry quality, phenolic content, and antioxidant activity [23, 24].

This review aims to explore the potential of probiotics and synbiotics as chemopreventive agents, focusing on their mechanisms of action, the evidence supporting their role in cancer prevention, and the future directions for research in this field. By delving into the complex interactions between diet, gut microbiota, and cancer, this review seeks to provide a comprehensive overview of how probiotics and synbiotics could contribute to innovative and effective cancer prevention strategies.

The Health Benefits of Probiotics and Their Role in Cancer Prevention

Cancer development is multifactorial, influenced by genetics, environmental carcinogens, lifestyle choices, and dietary habits [25]. Diets high in fats and sugars and low in fiber can lead to an imbalance of gut microbiota (dysbiosis), which is linked to numerous diseases, including cancer [11, 26]. For instance, a high intake of polyunsaturated omega-6 fatty acids may alter gut microbiota, leading to metabolic disturbances and obesity, thereby increasing cancer risks [27]. Dysbiosis can also trigger inflammatory and immune responses that facilitate cancer development [28, 29]. The native gut microbe, *Fusobacterium nucleatum*, has been shown to invade tumor cells and initiate tumorigenesis, highlighting the critical role of microbiota regulation in cancer prevention [30].

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have been reported to modulate gut microbiota in terms of enhancing barrier functions, reducing permeability, reducing systemic inflammation, preventing the translocation of potential carcinogens, and promoting an environment that is less conducive to cancerous growths (Table 1). Probiotics such as *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Streptococcus*, and *Enterococcus* have been claimed to enhance gut health by maintaining intestinal pH, producing hydrogen peroxide to inhibit pathogen growth, and synthesizing antimicrobial peptides, thus creating an environment detrimental to pathogenic bacteria and beneficial for the host [31]. For example, *Lactobacillus plantarum* UBLP40 produces hydrogen peroxide against pathogens like *Micrococcus luteus* MTCC 106 and methicillin-resistant *Staphylococcus aureus* subsp. *aureus* ATCC® BAA-1720 to prevent the proliferation of harmful microbial colonies that can contribute to cancer progression [32].

Some probiotics produce short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, which serve as energy sources for colonocytes and regulate cell proliferation and apoptosis in cancer cells [58]. SCFAs such as those produced by *Bifidobacterium animalis* subsp. *lactis* GCL2505 and *Lacticaseibacillus paracasei* SD1 have demonstrated anti-cancer properties and help maintain a healthy intestinal microflora [59, 60]. Probiotics also enhance the body's immune response against cancer cells by regulating cytokine production, which is critical for directing immune responses and improving surveillance and destruction of cancer cells. *Enterococcus faecium* S29 (EU 158,188) secretes antimicrobial compounds that compete with pathogenic bacteria in the gut mucosa, altering microbiota composition and reducing cancer development [61]. Similarly, the intake of *Lactobacillus gasseri* OLL2716: LG21 has been associated with a decrease in *Clostridium perfringens* levels (a bacterium linked to colorectal cancer) and an increase in beneficial SCFAs in the gut of colorectal cancer patients [62].

Moreover, probiotics play a role in enhancing mucin production and maintaining the integrity of the gut barrier. It is crucial for preventing the translocation of bacteria and

Table 1 Effects of probiotics on cancer cells

Strains	Type of cancer/cell lines	Effect	Reference
Bacillus polyfermenticus	Human colon cancer cell lines HT-29, DLD-1 and Caco-2	Inhibited cell colony formation	[33]
Bacillus polyfermenticus KU3	RAW 264.7 (murine macrophage cell line) MRC-5 (human lung cell line) HeLa (cervix cancer cell line) LoVo (human colon adenocarcinoma cell line) HT-29 (human colon adenocarcinoma cell line) AGS (human stomach adenocarcinoma cell line) MCF-7 (human breast adenocarcinoma cell line)	Inhibited cell proliferation	[34]
Bifidobacterium lactis KCTC 5727	HT-29 colon cancer cells	Reduced tumor incidence Reduced tumor volume	[35]
Clostridium butyricum ATCC Bacillus subtilis ATCC 9398	Human colon cancer cells HCT116, SW1116 and Caco-2 cells	Inhibited cell proliferation	[36]
Enterococcus faecalis CECT7121	LBC cells	Inhibited proliferation of tumor cells Induced apoptosis	[37]
Escherichia coli KUB-36	Colorectal cancer cells HT-29 Human breast cancer cells MCF-7 Human normal breast cell MCF-10 A	Inhibited cell proliferation	[38]
Lactobacillus acidophilus 606	Colorectal cancer cells HT-29	Inhibited cell proliferation	[35]
Lactobacillus acidophilus CL1285 *Lactobacillus casei* LBC80R	LS513 colorectal cancer cells	Induced apoptosis	[39]
Lactobacillus acidophilus KFRI342	DMH-induced colon cancer	Reduced β-glucuronidase and β-glucosidase activity	[40]
Lactobacillus casei ATCC 393	Murine (CT26) and Human (HT29) colon carcinoma cell lines	Inhibited cell proliferation Induced apoptosis	[41]
Lactobacillus kefiri P-IF	Human multidrug-resistant (MDR) myeloid leukemia (HL60/AR) cells	Induced apoptosis	[42]
Lactobacillus paracasei IMPC2.1 *Lactobacillus rhamnosus* GG	HGC-27 gastric and DLD-1 colon cell lines	Inhibited cell proliferation Induced apoptosis	[43]
Lactobacillus pentosus B281 *Lactobacillus plantarum* B282	Human colon adenocarcinoma cell lines Caco-2 and HT-29	Inhibited cell proliferation Induced G1-phase arrest Down-regulation of cyclin genes	[44]
Lactobacillus plantarum (AdF10) *Lactobacillus rhamnosus* GG	DMH-induced colon cancer	Reduced tumor incidence Reduced tumor volume Reduced tumor multiplicity	[45]
Lactobacillus plantarum A7 *Lactobacillus rhamnosus* GG	Human colorectal adenocarcinoma cell line Caco-2 Colorectal cancer cells HT-29	Inhibited cell proliferation	[46]
Lactobacillus plantarum NCU116	Colorectal carcinoma	inhibited the proliferation of cancer cells induction of apoptosis increased the expression of pro-apoptotic genes	[47]
Lactobacillus rhamnosus GG *Bifidobacterium lactis* Bb12	Colorectal cancer cells HT-29	Induced apoptosis	[48]
Lactobacillus rhamnosus GG Bifidobacterium lactis Bb12	Human colorectal cell line Caco-2	Induced apoptosis	[49]
Lactobacillus rhamnosus GG CGMCC 1.2134	DMH-induced colon cancer	Reduced tumor incidence Reduced tumor volume Reduced tumor multiplicity Induced apoptosis	[50]
Lactobacillus rhamnosus GG MTCC #1408 *Lactobacillus acidophilus* NCDC #1	DMH-induced colon cancer	Reduced tumor incidence Reduced tumor multiplicity	[51]
Lactobacillus salivarius Ren	DMH-induced colon cancer	Reduced tumor incidence	[52]

Table 1 (continued)

Strains	Type of cancer/cell lines	Effect	Reference
Lactococcus lactis NK34	RAW 264.7 cells (murine macrophage cell line) MRC-5 cells (human lung cell line) SK-MES-1 cells (human lung carcinoma cell line) DLD-1, HT-29, LoVo cells (human colon adenocarcinoma cell line) AGS cells (human stomach adenocarcinoma cell line) MCF7 cells (human breast adenocarcinoma cell line)	Inhibited cell proliferation	[53]
Pediococcus pentosaceus FP3 *Lactobacillus salivarius* FP25/FP35 *Enterococcus faecium* FP51	Human colorectal adenocarcinoma cell line Caco-2	Inhibited cell proliferation Induced apoptosis	[54]
Pediococcus pentosaceus GS4	Human colon cancer cells HCT116	Inhibited cell proliferation Induced apoptosis	[55]
Pediococcus pentosaceus M41	Human colorectal adenocarcinoma cell line Caco-2 MCF-7 cells	Inhibited cell proliferation	[56]
Propionibacterium freudenreichii ITG P9	HGT-1 human gastric cancer cell	Induced apoptosis	[57]

harmful metabolites into the systemic circulation, which could lead to systemic inflammation and cancer [63]. *Escherichia coli* Nissle 1917 had been reported to inhibit the leaky gut condition by upregulating the zonula occludens-1 (ZO-1) in murine intestinal epithelial cells [64]. *Lactobacillus casei* GG has been shown to inhibit the translocation of specific pathogenic bacteria by upregulating the MUC2 gene expression, contributing to maintaining the gut barrier integrity [64]. Probiotics, such as *Lactobacillus rhamnosus* GG, have been shown to suppress procarcinogenic fecal enzymes like azoreductase, nitroreductase, and β-glucuronidase, which can convert procarcinogens into carcinogens [65]. *Lactobacillus rhamnosus GG* suppresses DMH-induced procarcinogenic fecal enzymes and preneoplastic aberrant crypt foci in early colon carcinogenesis [51, 66]. Lactulose and OF-IN significantly decreased beta-glucuronidase activity, whereas a tendency to a decreased beta-glucuronidase activity was observed after *L. casei* Shirota intake [51, 67, 68].

Probiotics have also been reported to inhibit cancer cell proliferation and induce apoptosis directly. Probiotics interact with and decrease toll-like receptors (TLR) on epithelial cells, macrophages, and lymphocytes, as well as regulate the synthesis of interleukin-10 (IL-10) and immunoglobulin A antibodies (IgA) to eradicate pathogenic bacteria in the intestine [69, 70]. For instance, *Lactobacillus casei* KCCM11072P (LC11072) exhibits antiproliferative activity against gastric cell lines by inhibiting NF-κB and mTOR-mediated signaling [71, 72]. The study demonstrates that the cell-free supernatant of *Enterococcus faecalis* KUMS-T48 displayed cytotoxic effects on gastric cancer cell lines [73]. Beyond these cellular effects, probiotics can also bind to and degrade carcinogenic substances in the intestinal lumen, reducing their potential harm [74]. *Saccharomyces* have demonstrated clinical and experimental effectiveness in gut diseases such as antibiotic-associated diarrhoea, Crohn's disease, and irritable bowel syndrome [75]. *Saccharomyces cerevisiae* var. *boulardii* has been shown to protect the normal microbiota of the human gut, inhibit pathogenic infections, and exhibit immune-modulatory properties, making it beneficial for managing irritable bowel syndrome [76].

Synbiotics: Combining Probiotics and Prebiotics with Chemopreventive

Synbiotics, which synergistically combine probiotics and prebiotics, enhance the survival and efficacy of beneficial gut bacteria, offering significant chemopreventive benefits (Table 2). By pairing live beneficial microbes (probiotics) with non-digestible fibers (prebiotics), synbiotics ensure better microbial survival through the harsh gastric environment and improve colonization in the colon [77, 78]. It is critical in cancer prevention, as synbiotics effectively maintain a balanced gut microbiota, crucial for reducing systemic inflammation (a known factor in cancer progression). Synbiotics can be either complementary or synergistic. A complementary synbiotic comprises probiotics and prebiotics that interact separately to accomplish one or more health advantages. In contrast, in a synergistic synbiotic, the prebiotics are selected to increase the activities of the co-administered probiotics. For instance, lactulose (prebiotic) that does not promote the growth of *Lactobacillus plantarum* has been combined as a complementary synbiotic with *L. plantarum* to reduce colibacillosis in pigs [79]. L-arginine boosted the

Table 2 The synbiotic combinations and their benefits

Types of synbiotics	Probiotic	Prebiotic	Benefits	References
Complementary synbiotics	*Lactobacillus acidophilus* LA-5®	Djulis (*Chenopodium formosanum*)	• Reduced total aberrant crypt foci (ACF) • Downregulated cancer-expressed genes • Regulated apoptosis-related proteins	[81]
	Lactobacillus casei strain Shirota and *Bifidobacterium breve* strain Yakult	4G-β-Galactosyl-sucrose	• Downregulates genes that are associated with inflammation and tumorigenesis	[82]
	Lactobacillus plantarum strain JC1 (B2028)	Lactulose	• Controls postweaning colibacillosis in pigs	[79]
	Lactobacillus plantarum 7–40 (NTU102)	Cacao pod husk pectin	• Increased the growth and enhanced immune response in *Litopenaeus vannamei* (shrimp)	[83]
	Lactobacillus reuteri 100 − 23	Inulin-type fructans	• Reduced proliferation of hepatic cancer cells, muscle wasting, and morbidity in leukaemic mice	[84]
	Lactobacillus plantarum ATCC 14,917	Delignified wheat bran	• Prevented contamination against yeasts, fungi, and coliforms	[85]
	Lactobacillus rhamnosus GG	Salicylic acid	• Display cytotoxic properties	[86]
Synergistic synbiotics	*Bacillus* sp. SJ-10	B-glucooligosaccharides	• Ameliorate the growth performance and natural immunity through gene expression and defend fishes against infectious *Streptococcus*	[87]
	Bacillus coagulans MTCC 5856	Plant sugar cane fiber	• Displayed anti-inflammatory effect • Modulated SCFAs profiles	[88]
	Bacillus coagulans Unique IS2	Inulin	• Reduce levels of C-reactive protein, increases glutathione levels	[77]
	Bifidobacteria lactis (BL-04)	Oligofructose/inulin	• Increased apoptosis • Reduced proliferating cell nuclear antigen (PCNA), p53 labelling indexes and development aberrant crypt foci (ACF) • Lower genotoxicity of fecal water	[89]
	Bifidobacterium longum 913	Oligofructose, inulin	• Prevents the development of pre-neoplastic lesions	[77]
	Bifidobacterium lactis HN019 *Lactobacillus casei* LPC-37 *Lactobacillus rhamnosus* HN001 *Lactobacillus acidophilus* NCFM	Fructooligosaccharide	• Significant reduction in IL-6 levels and CRP.	[90]
	Bifidobacterium bifidum (ATCC 29,521) *Lactobacillus acidophilus* (ATCC 4356) *Lactobacillus delbrueckii* ssp. *bulgaricus* (ATCC 11,842) *Lactobacillus plantarum* (ATCC 14,917) *Lactobacillus rhamnosus* (ATCC 7469)	Inulin	• Reduce intrahepatic triacylglycerol	[91]
	Lactobacillus acidophilus ATCC® 4357™	Fructooligosaccharide and isomaltooligosaccharide	• Displayed significant antimicrobial and antidiabetic properties	[92]
	Lactobacillus acidophilus ATCC 4962	Fructooligosaccharide, mannitol, inulin	• Reduce overall cholesterol and low-density lipoprotein cholesterol	[93]
	Lactobacillus brevis KU200019	Fructooligosaccharide	• Possess angiotensin-converting enzymes-inhibitory properties, antioxidant effect, immunomodulatory activity	[94]
	Lactobacillus bulgaricus 6c3 Strain	Inulin, fructooligosaccharide	• Reduce indoxyl sulfate • Reduce renal fibrosindoxyl sulfate	[95]
	Lactobacillus rhamnosus GG (LrG)	L-arginine	• Suppress the growth of *Streptococcus mutans* and can develop as an anti-caries therapy	[80]

Table 2 (continued)

Types of synbiotics	Probiotic	Prebiotic	Benefits	References
	Lactobacillus plantarum NCIMB 8826 (Lp8826) *Lactobacillus fermentum* NCIMB 5221 (Lf5221) *Bifidobacteria longum* spp. *infantis* NCIMB 702,255 (Bi702255)	Triphala	• Enhanced the motility of *Drosophila melanogaster*	[96]
	Lactobacillus plantarum S58	Hull-less barley β-glucan	• Refined the lipid accumulation • Suppressed inflammation • Stimulated the discharge hormones involved in lipid metabolism • Activated 5′ monophosphate-activated protein kinase signalling in high-fat diet-fed mice	[97]
	Lactobacillus paracasei B21060	Fructooligosaccharide and arabinogalactan	• Preserve epithelial barrier integrity • Induce tissue repair • Provide gut protection • Reduce inflammation and oxidative stress	[98]
	Lactobacillus plantarum ATCC 8014	Inulin	• Increase antioxidant capacity	[99]
	Lactobacillus plantarum ATCC 8015	Inulin	• Reduce cardiac apoptosis and fibrosis in type 2 diabetes mellitus	[100]
	Lactobacillus plantarum NCIM 2083	Sulfated polysaccharides	• Displayed anti-tumor properties • Inhibition of colon cancer cells	[74]
	Bifidobacterium lactis Bb12 *Lactobacillus delbreuckii* subspecies *rhamnosus* strain GG	Oligofructose-enriched inulin	• Reduced colorectal proliferation and capacity of fecal water • Improve epithelial barrier function • Decreases exposure to genotoxins • Prevented an increased secretion of interleukin 2 • Increased the production of interferon γ	[74]
	Weissella cibaria FB069	Xylooligosaccharides	• Displays antiproliferative activities against human colon adenocarcinoma cells, human colorectal carcinoma cell line cells	[101]

growth and survival of *Lactobacillus rhamnosus* and was combined as a synergistic synbiotics [80].

Some believe synbiotics are more beneficial than either probiotics or prebiotics alone because synbiotics display the qualities of both components [102, 103]. Studies suggest synbiotics may prevent and improve the health of diabetic individuals by enhancing the beneficial gut microbiota composition [104]. Diabetes occurs when insufficient insulin is produced, reducing nitric oxide bioavailability and developing endothelial dysfunction. Synbiotic fermented milk of *Lactobacillus acidophilus* ATCC® 4357™ with fructooligosaccharide and isomaltooligosaccharide efficiently reduces blood glucose levels [92]. A positive effect on reducing liver injury and insulin resistance was also reported in high-fat diet-induced rats treated with synbiotics of *Lactobacillus paracasei* B21060, arabinogalactan, and fructooligosaccharides [105]. Moreover, synbiotic supplements remarkably decreased insulin and fasting blood sugar levels [106]. Synbiotic food resulted in a notable increase in the production of plasma nitric oxide [107, 108]. Nitric oxide is a ubiquitous signalling molecule that contributes to the synthesis and secretion of insulin [109]. It was suggested that synbiotics improved endothelial nitric oxide synthase activity in umbilical vein endothelial cells. The synbiotic treatment also improved hormonal homeostasis and glycemic control and decreased the synthesis of inflammatory cytokines and phosphorylation in the insulin receptor in high-fat diet-induced rats [105, 110].

Patients with diabetes are likely to suffer from heart-related diseases [111], which can be alleviated by consuming synbiotic supplements to lower systolic and diastolic blood pressure [110]. The improvement in blood pressure in diabetics may be due to an improvement in nitric oxide production via probiotic actions. The increment of nitric oxide may aid the blood vessels in relaxing and maintaining low systolic and diastolic blood pressure [112]. The synbiotic effect of *L. sporogenes* and inulin reduces very low-density lipoprotein cholesterol and triacylglycerol [113]. A study using *Enterococcus faecium* CRL 183 and *Lactobacillus helveticus* ssp. *jugurti* 416 in combination with soybean and yacon extract revealed a reduction in triglyceride and total cholesterol levels, as well as a substantial increase in high-density lipoprotein (HDL) cholesterol in the treatment group [114]. High production of HDL cholesterol prevents the build-up of low-density lipoprotein (LDL) cholesterol, in which high LDL cholesterol content may deposit in the walls of the blood vessels and arteries, leading to atherosclerosis and heart attack. Reducing cholesterol levels is suggested due to the digestion and absorption of cholesterol in the intestine by the probiotics in the synbiotics [114]. Incorporating prebiotics in synbiotics further uplifts the probiotic's survival and mechanism of action, enhancing cholesterol absorption in the small intestines.

The chemopreventive actions of synbiotics include enhancing gut barrier function to prevent the translocation of pathogenic bacteria and toxins, modulating immune responses to detect better and eliminate cancer cells, reducing exposure to carcinogens by altering gut pH and microbial environment, and promoting anti-inflammatory effects through the production of short-chain fatty acids like butyrate, propionate, and acetate [77]. These fatty acids are particularly effective in inhibiting tumor cell proliferation and inducing apoptosis. Clinical studies underscore the potential of synbiotics in reducing biomarkers of cancer progression, particularly in colorectal cancer, where they have helped decrease the incidence of polyps and adenomas. Furthermore, synbiotics are being explored for their role in supporting cancer treatment regimens, such as chemotherapy, by alleviating adverse effects like diarrhea and mucositis and maintaining gut integrity. Synbiotics of *Lactobacillus acidophilus* LA5 and *B. animalis* subsp. *lactis* BB-12 with germinated brown rice induced cancer cell apoptosis, thus suppressing colon tumor growth [115]. The chemopreventive effects of synbiotics (*Lactobacillus gasseri* 505 and *Cudrania tricuspidata* leaf extract) were also proven in in vivo studies on colitis-associated colorectal cancer mice [116]. Synbiotic-treated mice produce higher levels of SCFAs, suppressing the *Staphylococcus* linked to intestinal inflammation and colorectal cancer [117]. As a result, the inflammation and carcinogenesis in colorectal cancer tissues were decreased [117]. A notable increase of tumor necrosis factor-α production and apoptosis-regulating genes were also observed in the synbiotic-treated mice; the production of anti-apoptosis genes and tumor cell proliferation significantly decreased in the synbiotic-treated mice simultaneously [117]. Consequently, synbiotic-treated mice exhibited enhanced tumor repression and reduced cancer cell proliferation [117].

Recent Technologies and Mechanisms Involved in the Gut Microbiota Function

Growing evidence demonstrates gut microbiota's significance in regulating anti-cancer treatments' efficacy and toxicity [118]. Besides the commonly known food supplements for gut microbiota improvement, emerging techniques such as fecal microbiota transplantation (FMT) and bacteriophage exhibited promising strategies in modulating the involvement of gut microbe involvement in chemoprevention and cancer treatments.

Faecal Microbiota Transplantation (FMT)

FMT, or fecal microbiota transplantation, involves transferring fecal material from a healthy donor to a recipient who

lacks a healthy gut microbiota composition. It has been found to significant advantages in immunotherapy as it reduces the side effects of treatment [119, 120]. FMT contributes to cancer prevention by restoring microbial diversity, reintroducing beneficial microbes, enhancing immunological function and tolerance, and detoxifying dietary carcinogens.

As previously mentioned, the gut microbiome plays a crucial role in modulating immune response and balance. An imbalance in gut microbiota is strongly associated with chronic inflammation and ultimately contributes to the development of cancer [121]. FMT enables patients to restore normal gut function by receiving a well-balanced microbiome from a donor [122]. The reintroduction of a selective beneficial gut microbiome through FMT alleviates disease symptoms, significantly minimizing the risk of cancer development. The beneficial microbes can produce various metabolites involved in the gastrointestinal tract's homeostasis balance [95, 123]. In addition, the production of anti-carcinogenic metabolites such as SCFAs, EPS, and bacteriocin can eliminate pathogenic bacteria by induction of apoptosis and inhibiting cancer growth. The enriched microbiome from donors possesses hydrolytic enzymes that could rapidly break down and eliminate dietary carcinogens before they can destroy the gut intestinal lining and hence inhibit cancer development [124]. FMT from a donor with a microbiome adept at this detoxification process can equip the recipient's gut with these beneficial bacteria. Thus, this improves the recipient's ability to neutralize dietary carcinogens and reduces cancer risk [125].

FMT has been successfully utilized to treat *Clostridioides difficile* infections (CDI) [126], inflammatory bowel disorders [127], autism [128], chronic kidney disease, metabolic syndrome [129], and alteration of hepatitis B virus infection [130]. Foremost, an in-depth systematic review of the global incidence of FMT to treat CDI demonstrated that FMT appears safe in major indication conditions with mild or moderate adverse events [129, 131]. It has been shown that FMT improves the effectiveness of anti-programmed death-1 (PD-1) therapy in melanoma patients [132, 133]. Anti-PD-1 therapy is an immunotherapy for metastatic melanoma that utilizes antibodies PD-1 to prevent the interaction of PD1 and release $CD8^+$ T cells from inhibition, thereby increasing anti-cancer activity. A combination of responder-derived FMT and anti-PD-1 therapy has shown clinical success in 30–40% of previously immunotherapy-refractory patients [133]. FMT and anti-PD-1 improved $CD8^+$ T cell activation and changed gene expression inside the tumour microenvironment, indicating that gut microbiota modification with FMT could be a way to enhance anti-PD-1 treatment [133]. Furthermore, FMT minimises the severity of side effects from cancer treatment by restoring balance and reversing the loss of diversity in gut microbiota after cancer treatment [127]. A positive result was reported in the study of *Bifidobacterium* strains in improving the immunopathology associated with cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade. *Bifidobacterium* was reported to reduce autoimmunity after checkpoint blockade therapies without reducing the anti-cancer responses [134].

Despite FMT showing some promising features, it has some limitations that need refinement. For example, there are no standardization approaches to FMT. Various aspects, such as delivery methods, stool preparation, and donor selection, need to be considered. Limited data is available to pinpoint which gut bacteria are responsible for the treatment's success or failure. The strongest evidence currently supports FMT's effectiveness is limited to treating recurring CDI. However, the application of FMT for other disorders like metabolic syndrome, inflammatory bowel disease, digestive problems, and obesity is still in the pioneering research stage. Clinical trial results are inconsistent, limiting our understanding of the gut microbiome's makeup and function. Therefore, this highlighted the need for a more precise and personalized approach to isolating and transferring beneficial bacteria. In short, FMT, as a potent medical procedure for the manipulation of gut health balance, holds great promise to reduce the risk of cancer and side effects. However, fortifying more understanding of the gut bacteria involved is important, and personalizing the treatment for better results across different diseases is important.

Bacteriophages

Bacteriophage therapy, or phage therapy, is a therapeutic approach that utilizes bacteriophages to combat bacterial infections. The mode of action of bacteriophage therapy involves attack, transfer, replication, and lysis. Initially, the bacteriophages target a susceptible host, followed by the transfer of genetic materials within the host, rapid replication, and, ultimately, the bursting of bacterial cells through lysis. Releasing new phages from the burst cells restores the phage attack cycle [135].

Recent advancements in understanding the role of bacteriophages in the gut microbiota have provided insights into their significance in human health. The interaction between bacteriophages and gut bacteria can contribute to the prevention of intestinal dysbiosis and associated diseases [136]. Changes in the gut microbiota have been associated with conditions such as ulcerative colitis, highlighting the impact of bacteriophages on gut health [137]. Extensive research has been conducted on the potential clinical applications of bacteriophages, including treating antibiotic-resistant bacteria in lung infections, and bone and joint problems [138, 139]. Studies have demonstrated that bacteriophages play a crucial role in preventing the formation of biofilms on medical devices [140]. Research has also indicated that bacteriophages have a dynamic influence on the gut microbiome

through predation and gene transfers, affecting the ecological structure of gut bacteriophages and their role in diseases like inflammatory bowel disease [141, 142].

On the other hand, bacteriophage therapy is essential in maintaining gut homeostasis, detoxifying carcinogens, and modulating the immune system [143]. Bacteriophage therapy has proven effective in controlling the carcinogenic microbiome [144]. By assembling nanoparticles on their surface, bacteriophages can kill *Fusobacterium nucleatum* and activate immune cells, leading to a stronger anti-tumor immune response [145]. However, chemotherapy may still be more evident and compelling than bacteriophage treatment. Moreover, dietary modulation of bacteriophages can potentially impact the gut microbiome, reducing the risk of gastroenteritis, inflammatory bowel disease, and cancer [146]. The versatility of phages in medical applications is demonstrated by their investigation for use in vaccine development and immunotherapy [147]. Each phage has a specific target bacterial host, allowing it to infect and replicate within a particular type or strain of bacteria [148]. This targeted approach selectively eliminates the target bacterial host with minimal disruption to the gut microbiome [149, 150]. The gut phageome of healthy individuals is believed to play a critical role in maintaining a healthy gut ecosystem [123]. The escalating threat of antibiotic resistance, caused by the emergence of antibiotic-resistant bacteria (ARB) and antimicrobial resistance genes (AMR), necessitates alternative treatment options [151]. Phages can be effective against bacteria resistant to conventional antibiotics, providing a potential solution to the growing problem of antibiotic resistance. In conclusion, phage therapy is gaining increasing attention as a potential alternative or complementary treatment for bacterial infections and antimicrobial resistance. However, further research and development are required to establish its broader use and effectiveness.

Probiotics and Drug Interactions

Understanding interactions between probiotics and drugs is essential, especially for cancer patients undergoing chemotherapy. Probiotics may influence the pharmacokinetics of chemotherapy drugs by modulating drug metabolism and altering drug absorption, distribution, and excretion [152]. Furthermore, probiotics could affect the efficacy and toxicity of chemotherapy by mechanisms such as enzyme modulation and competition for binding sites [153].

In the context of irinotecan (a cancer drug), there are positive and negative interactions with gut microbiota. Gut bacteria such as *Bacteroides vulgatus*, *E. coli*, and *Clostridium ramosum* may produce β-glucuronidase, which transforms SN-38 G (an active metabolite) into SN-38 (an inactive metabolite that may cause neutropenia and diarrhea), thereby increasing the risk of side effects and reducing the effectiveness of cancer treatments. Contrarily, probiotics such as *Lactobacillus reuteri* and *Bifidobacterium infantis* do not affect the therapy with irinotecan as they lack the gene to produce β-glucuronidase. Administrating a bacterial β-glucuronidase inhibitor shielded the mice from gastrointestinal toxicity, indicating that microbial β-glucuronidase inhibitor could be clinically used to improve drug efficacy and minimize the side effects (154). VSL3 (the combination of *Lactobacilli* spp., *Bifidobacteria* spp., and *Streptococcus thermophilus*) has also been found to reduce irinotecan-induced diarrhea in animal studies by promoting the growth of intestinal cells and preventing cell death [155]. *Bifidobacterium longum* enriched with selenium has shown promise in reducing the risk of irinotecan-induced diarrhea in mice by enhancing enzyme activity and increasing gene expression [156, 157].

Beyond the interactions with cancer drugs, probiotics may enhance the effectiveness of antibiotics by maintaining a balanced gut microbiota, which potentially lowers the risk of infections during cancer treatment. For instance, the use of synbiotics (inulin, *Lactobacillus rhamnosus*, and *Bifidobacterium lactis*) has been found to reduce colorectal proliferation significantly, induce necrosis in colonic cells and increase the production of interferon γ in the cancer patients [74]. Clinical studies have also revealed positive outcomes when cancer patients took synbiotics after colorectal cancer surgery, including fewer infections, less diarrhea, quicker recovery of normal gut function, reduced use of antibiotics, lower risk of severe infections, and shorter hospital stays [158, 159].

Furthermore, probiotics have the potential to alter the immune system and increase the body's response to vaccines, which could have implications for cancer prevention. Probiotics have been shown in studies to improve vaccine-induced immune responses. *Bifidobacteria* and *Lactobacillus* have been shown to boost seroconversion and seroprotection rates in adults receiving influenza vaccines, as well as increased interferon- (IFN-) production and better antibody responses in infants following Hepatitis B immunization [160–162]. Other probiotic strains like *E. coli*, *Lactococcus lactis*, and *Bacillus* species have also demonstrated the ability to bolster humoral and cellular immune responses [163–165].

Probiotics are also reported to assist in detoxifying the gut, potentially reducing the risk of cancer associated with pesticide exposure and heavy metals. *Lactobacillus* was found to sequester organophosphate pesticides, parathion, and chlorpyrifos. Remarkably, this pesticide-sequestering capability was observed to be independent of the metabolic activity of the bacteria, with both live and heat-killed *Lactobacillus* strains demonstrating similar pesticide-capturing abilities [166]. Numerous in vitro studies have also been conducted to

investigate the potential of probiotics to exhibit detoxification properties, such as *Lactobacillus plantarum* on chromium, cadmium, and lead toxicity [167–169], *Bacillus cereus* on cadmium toxicity [170], and *Lactobacillus* on mercury toxicity [171]. These probiotics enhance the elimination of heavy metals from the body, reversing their adverse effects on gut microbiota.

Potential Challenges and Future Directions

Despite the growing body of research supporting probiotics in cancer prevention and treatment, several challenges and questions remain. The effects of probiotics can be highly strain-specific, necessitating further research to identify the most effective probiotic strains for cancer prevention and treatment. Determining optimal dosages and treatment durations and standardizing probiotic products in terms of quality, quantity, and labelling is essential to ensure consistent and reliable results across studies [77]. While probiotics are generally considered safe, certain patient populations, such as those with compromised immune systems, may be at risk of adverse effects, emphasizing the need to establish safety profiles for specific groups. Genetic stability, deleterious metabolic activity, and potential pathogenicity of probiotics over time must also be assessed according to the probiotics involved, particularly immunological effects in infants. Probiotics have been reported to confer infections by translocation throughout the digestive tract and intestines [172]. Individuals with weak immune responses, specifically long-term hospitalized patients, have an increased risk for infection. Lactose intolerant individuals might also experience bloating and gas issues upon consuming synbiotic food consisting of lactose due to D-lactic acidosis and the overgrowth of bacteria in the small intestines [173]. Biogenic amines, often released from fermented probiotic-based food products, have been reported to fluctuate and rise or reduce blood flow, which might trigger headaches in individuals [174].

As personalized medicine advances, tailoring probiotic usage based on an individual's gut microbiota and genetic makeup may become an exciting avenue. One of the most significant innovations is the application of CRISPR-Cas systems. The CRISPR-Cas systems are being used in probiotics for cancer treatment by leveraging the ability of certain probiotic bacteria to colonize tumor regions and deliver the CRISPR-Cas9 system to the tumor site. It has been demonstrated *Lactobacillus rhamnosus* GG (LGG) can penetrate the hypoxia tumor center, allowing efficient delivery of the CRISPR-Cas9 system to the tumor region [175]. The process of genetically modifying probiotics involves several key steps: designing a specific guide RNA (gRNA) to target a desired DNA sequence within the probiotic, using the Cas9 enzyme to create a precise cut at the DNA target site, and then allowing the bacterial cell to repair the cut using its natural mechanisms, which can be harnessed to introduce or disrupt genes [176]. In the study by [175], the CRISPR-Cas9 system is used to knockdown tumor immunosuppression-related genes, which helps to amplify immunogenic cell death and reverse tumor immunosuppression. Consequently, *Lactobacillus rhamnosus* GG (LGG) efficiently colonizes the tumor area and activates the immune system, thus, enhancing the effectiveness of the CRISPR-Cas9 system in inducing ICD and lifting immunosuppression. It has been shown that the CRISPR-Cas9 system generates immune responses that effectively attack tumor cells in mice, contributing to the inhibition of tumor re-challenge in vivo, providing an immunological memory effect, and offering protection against lung metastasis [175].

The emerging of single-cell RNA sequencing (scRNA-seq) technologies also improves our understanding of gut microbiome and cancer relationship [176]. The study of gene profiles at the individual microbial cell provides the vast heterogeneity within microbial communities and sheds light on their potential roles and interactions in cancer pathology, particularly in how they influence the tumor microenvironment [177]. For example, scRNA-seq has been reported to profile the transcriptomes of cells, which helps understand the cellular landscapes of tumors and the development of personalized cancer treatments. It is suggested that these detailed profiles can be used to tailor therapies based on the specific cellular makeup of each patient's tumor, potentially increasing the efficacy of treatments and reducing side effects [178]. The scRNA-seq has been claimed in advancing the cellular mechanisms and genetic mutations that facilitate resistance, leading to a better understanding to design therapies that improve patient therapeutic outcomes [179]. Additionally, scRNA-seq has been applied to study circulating tumor cells (CTCs), which are essential for understanding cancer metastasis and progression. Analyzing the gene expression profiles of CTCs at the single-cell level could enriche the comprehension of tumor biology and metastatic processes, offering for new therapeutic interventions [176]. To date, scRNA-seq has identified various cell populations within lung tumors, some of which are associated with poor prognosis; uncovered cellular heterogeneity and mechanisms of drug resistance in breast cancer; and identified cell populations linked to poor prognosis and drug resistance in ovarian cancer [179].

Conclusion

The genetic makeup in the gut microbiota is 100 times greater than that of humans. Gut microbes compensate for the weakness of humans' metabolism by providing valuable metabolites through catabolism and anabolism reactions. Therefore, synbiotics have emerged as new functional foods

for healthy immune balance. However, the minimal intake of probiotics and prebiotics to exert their maximum function is still debated. The technology to maintain, process, and mass produce synbiotic products for market demand are the critical aspects that need to be considered for overall benefits. Various technologies to formulate synbiotics in food products should be studied in depth. Omics technology allows the pathophysiology study of synbiotics to explain the health diseases and prevention mechanisms. Further, in vitro and in vivo clinical studies are also required to analyze the effect of synbiotic consumption in individuals with various health problems, which could provide sound evidence for maximum utilizing probiotics in treatments.

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Declarations

Competing Interests The authors declare no competing interests.

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