Review

Microbiome Modulates Immune System to Influence Cancer Therapy

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Microbiome Modulates Immune System to Influence Cancer Therapy

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Simple Summary: This review discussed the importance of gut microbiome for cancer patients and how the disturbance in microbiome can lead to unwanted side effects during the cancer treatment. How the variety of food can influence the microbiota and its abundance has been described. Not only this, the effect of antibiotics can also modulate the abundance of gut microbiome and its diversity. Alteration in the bacterial population can help in achieving better immune responses and maintain the intestinal barrier integrity. In this regard, this article also discussed several advanced approaches utilizing the advantage of probiotics along with immunotherapies.

Abstract: Gut microbiota composition can affect tumor microenvironment and its interaction with the immune system, thereby having implications on treatment predictions. This article reviews the studies available to better understand how gut microbiomes help the immune system to fight cancer. To describe this fact, different mechanisms, and approaches of utilizing probiotics to improve advancements in cancer treatment will be discussed. Moreover, not only the calorie intake but also the variety and quality of diet can influence cancer patient's immunotherapy treatment because dietary patterns could impair the immunological activities either by stimulating or suppressing the innate and adaptive immunity. Therefore, it is interesting and critical to understand the gut microbiome composition as a biomarker to decide cancer immunotherapy outcomes and responses. Here, more emphasis would be given to the recent development in immunotherapies utilizing microbiota to improve cancer therapies which is beneficial for cancer patients.

Keywords: probiotics; microbiota; cancer immune therapy

1. Introduction

Cancer is the second leading cause of death worldwide according to the World Health Organization (WHO) affecting over 9 million people worldwide [1]. Epidemiological studies have shown that diet is crucial for influencing the risk of cancer. In 2009, WHO emphasized on the association of diet and lifestyle-related risk factors and the burden of diseases [2]. These factors include environmental stress, eating habits, alcohol, obesity, inappropriate physical activity, high blood glucose, cholesterol level, fruits and vegetables intake accounted for 18% and 25% of the world death burden in low -middle–income countries and high-income countries, respectively [2,3]. Therefore, studies are more focused on restricting the diet and energy intake to influence cancer development and its treatment [4]. Here, we describe the quality of diet that can influence cancer treatment and the biomarkers associated with digestive tract cancers. Although there are available therapeutic strategies to treat cancer patients, it's not completely enhancing their lifestyle or causing them to suffer associated side-effects. These treatments greatly impact on their day to day life due to pain associated with these strategies especially particularly chemotherapy and radiotherapy causing severe abdominal pain, diarrhea, mucositis, vomiting, constipation etc. [5]. These therapies alter the composition of intestinal microbiota i.e., dysbiosis leading to immunological dysregulation and sometimes resistance to some bacteria. For example, paclitaxel, a known chemotherapeutic agent not

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only affects the gut microbiome, colonic tissue integrity, microglia activation, but also increases some pro-inflammatory agents like matrix metalloproteinase 9 (MMP9) and tumor necrosis factor-alpha (TNF-α) levels that alter bacterial diversity in colon [6]. Nonetheless, gut microbiota may accelerate the development of cancer by several ways such as causing DNA damage, genetic alteration, or affecting cell cycle progression via its products or making protumorigenic microbial niches, including biofilms, or creating immune dysregulation.

Thus, in this article, we are discussing how any diseased condition or even the cancer development can make changes to the gut microbiota and its influence on immune responses. Moreover, how the side effects or symptoms associated with the cancer treatment can be cured or alleviated with the administration of probiotics can help or facilitate cancer treatment (Figure 1). Therefore, in this article, we discussed in detail how various treatment procedures involving the usage of live microorganisms (probiotics) or the dietary fibre fermented by intestinal microorganisms (prebiotics) are being studied and used to help growth and abundance of friendly bacteria to modify gut microbiota from dysbiosis to their homeostasis condition to control cancer progression.

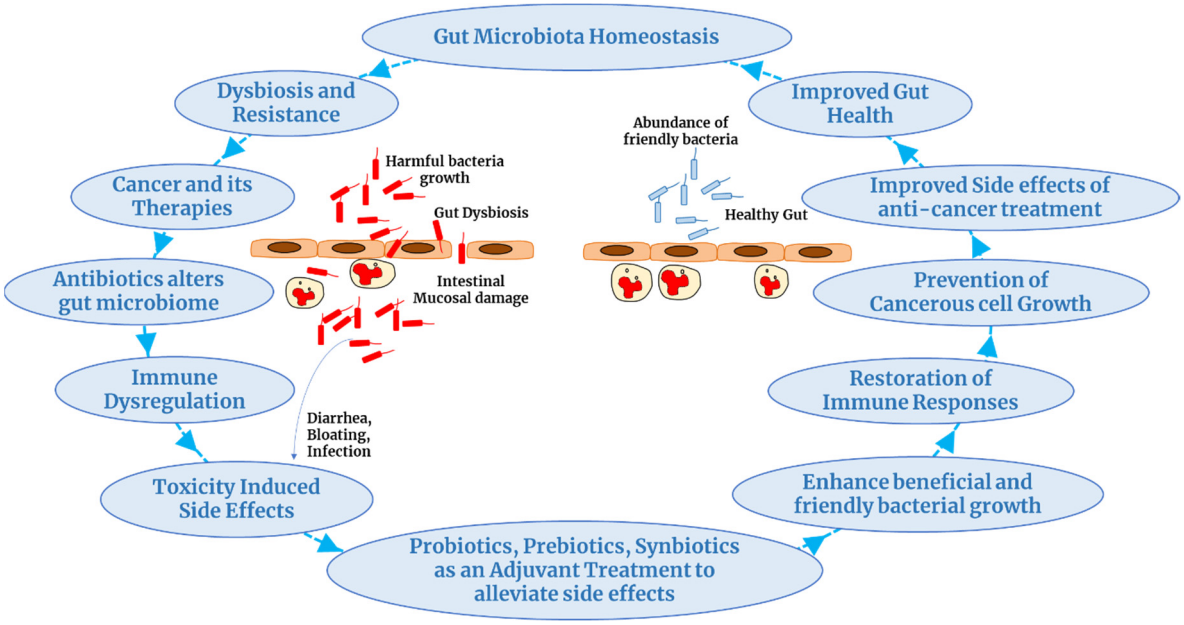

Figure 1. Manipulating the gut microbiota to alleviate cancer therapies side effects.

2. Quality of food increase risk of cancer

In 2018, World Cancer Research Fund has reported an inconclusive association of including fruits or vegetables in diet with the risk of any cancer [7]. Usually, the risk of cancer in vegetarians is less as compared to non- vegetarians because their diet is more dependent on fruit and vegetables than the non-vegetarians but this cannot be true for each and individual cancer type [8]. It is evident that long term health of vegetarians is comparatively better than the non-vegetarians due to lower prevalence of health issues such as weight gain, obesity, diabetes, stroke, and cancer. The intake of processed meat and cheeses could be one of the reasons for increasing cancer risk because of their high content of nitrite/nitrate [9,10]. Also, International Agency for Research on Cancer (IARC) in 2018 documented the toxic effects of processed or unprocessed meat due to the presence of haem iron, which leads to enhanced formation of nitroso compounds in the gastrointestinal tract e.g., S-nitrosothiols and the nitrosyl heme [11,12]. These nitroso compounds can alkylate guanine to form the promutagenic DNA lesions O^6-methylguanine and O^6-carboxymethylguanine. This mutation can cause cancer if not repaired. Moreover, cooking of meat at high temperatures can produce mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons that can also be one of the reasons to increase the risk of cancers [13].

A detailed study by Reynolds in 2019 explained the association between carbohydrate quality and human health by performing extensive meta-analyses of prospective studies and reviewing

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systematic published reviews from the database. Their findings based on thorough search of the literature available in database such as PubMed, Embase, Ovid MEDLINE, and the Cochrane Central Register of Controlled Trials, suggested higher intakes of whole grains were associated with a 15 to 30% reduction in the risk for all critical outcomes including cardiovascular associated mortality, colorectal cancer and type 2 diabetes [14]. High dietary folate [15] and high dietary fibre consumption can reduce the rate of colorectal cancer. Especially cereal fibre and wholegrain cereals are more protective than fibre from fruit or vegetables [14,16]. However, dietary fibres are controversial and classified as probable causes of cancer as per World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) [9]. Reports from WCRF and AICR provide updates on specific cancers and guidance for cancer patients and survivors on diet and lifestyle changes. These reports also benefit individuals who are at risk due to genetic predisposition or carcinogenic exposures [17]. Among the most probable causes associated with cancer risk is alcohol consumption through the development of cirrhosis and alcoholic hepatitis. Second most probable cause of inducing cancer is overweight and obesity [18]. Association between vegetable intake and cancer risk was established among women but not observed among men. A detailed study including several parameters such as age, sex, smoking, energy intake, ethnicity and other potential dietary factors. This study revealed higher intake of non-starchy vegetables, salt, pickled food, and processed meat is inversely associated with the risk of bladder and gastric cancer [19–21].

Foods containing vitamin C, calcium supplements [22] and folate supplements help to suppress the development of tumors in normal tissues [23]. Folate is required for DNA synthesis and replication and its deficiency can result in ineffective DNA synthesis and transformation of normal cells to neoplastic ones.

Similarly, consumption of coffee reduces cancer risk due to the presence of strong antioxidants and anti-inflammatory agents such as polyphenolic compounds. A bibliographic study by Pauwels et al, 2021 based on the search on PubMed and Embase identified that intake of coffee is inversely associated with risk of hepatocellular cancer and breast cancer among postmenopausal women [21]. The reason for this association and beneficiary effect of coffee ascribed to the presence of some bioactive components such as caffeine, cafestol, kahweol, and chlorogenic acids. The protective role of coffee was investigated and confirmed by another population-based case-control study where coffee was proposed as a protective factor for colorectal cancer because it reduces the cancer risk by 26% [24]. However, this search could comment clearly on this association with other cancer types including the esophagus, pancreas, colorectum, kidneys, bladder, ovaries, and prostate because the results were inconclusive, or the data were insignificant in those reports. Thus, clear evidence is needed before recommending any food or beverages consumption.

Mediterranean-style dietary pattern (MSDP) also strongly lowers the risk of cancer as shown in a semi-quantitative food frequency questionnaire-based exam involving 2966 participants of the Framingham Offspring who were free of prevalent cancer. This study has shown the beneficial association of MSDP on cancer risk. In this study, MSDP has a beneficial effect on women showing lower risk of cancer as compared to men who have higher adherence to MSDP [25].

Role of sugar and salt is important for the taste of food but if it is taken in a disproportionate amount then it can also lead to risk to health. A study by Wu et al., 2021 has performed a systematic review and meta-analysis to determine the association of salt intake with gastric cancer morbidity and mortality. This cohort study observed that high but not moderately pickled food intake increases the gastric cancer risk, whereas no effect of moderate or high salted fish intake was associated with gastric cancer risk. Moreover, it is advisable to not consume fermented Cantonese-style salted fish or high intake of processed meat can be associated with a higher risk of gastric cancer [26,27]. Another study by Strumylaite et al. 2006 has reported the consumption of salted mushrooms might increase the risk of gastric cancer for people that like salty food, salt-preserved meat as well as fish [28].

Contaminated food with certain fungi that are found on crops may also increase the risk of liver cancer. Toxin produced by *Aspergillus flavus* and *Aspergillus parasiticus* i.e., aflatoxins, which are abundant in warm and humid regions of the world is known to be associated with an increased risk of liver cancer [29]. Not only the contaminated food can be the cause of increasing risk to cancer,

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drinking water contaminated with arsenic can also cause solid cancers of lung, urinary bladder, skin, kidney, liver and prostate. Arsenic is a known carcinogen that can get into the body through exposure to arsenic contaminated drinking water. This was shown in a recent cohort study by Issanov, et al., 2023 and Lin et al., 2022, where they highlighted the relationship between arsenic in drinking water and the incidences of lymphoma and leukemia by sex, exposure category and time period [30,31]. These studies suggested that exposure to arsenic increases the risk of developing bladder and kidney cancers.

3. Gut microbiome and biomarkers for unfavorable microbiome

Human gut contains the largest population of microbes such as bacteria, viruses, protozoa, and fungi of biomass of 1.5 kg, which is influenced by several factors such as age, diet, gender, and environment [32,33]. Diet and gut microbiome are the deciding factor of human health. Microbial ecology, genotype and their proportion affect the energy and nutrient harvest. To understand these interrelations, a study model representing the human gut ecosystem was prepared by Turnbaugh et al., using germ-free C57BL/6J mice by transplanting fresh or frozen adult human fecal microbial communities. They observed altered microbiome gene expression, increased adiposity and changed representation of metabolic pathways in the microbiome after switching from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar "Western" diet [34].

Disturbance in the microbiome can result in disease conditions and its evidence can be found and discussed in this review (Table 1). Dectin-1 is a pattern-recognition receptor and innate immune response modulator protein that potentially serve as biomarkers to identify people with a potentially unfavorable gut microbiome. Dectin-1 gene expression in subcutaneous adipose tissue was investigated in the context of obesity and associated inflammatory markers. Results showed the correlation between the expression of dectin-1 transcripts and various proinflammatory cytokines, chemokines, and their cognate receptors in terms of body mass index, fat percentage and with monocyte/macrophage markers (CD16, CD68, CD86, and CD163). These results suggest Dectin-1 can be used as adipose tissue biomarker of metabolic inflammation in obesity [35].

Table 1. Prevalence of specific microbiota deciding cancer type.

Biomarkers	Cancer type	Abundance	Ref.
Veillonella, Fusobacterium, Prevotella, Porphyromonas, Actinomyces *and* Clostridium, Haemophilus, Enterobacteriaceae *and* Streptococcus *spp and* Candida albicans	oral carcinoma	Elevated in tumor sites	[36]
Capnocytophaga gingivalis, *Prevotella melaninogenica* and *Streptococcus mitis*	oral squamous cell carcinoma (OSCC)	Elevated in the saliva of individuals with OSCC	[37]
Fusobacterium nucleatum, S salivarius: Streptococcus vestibularis, Prevotella oris, and *Rothia mucilaginosa*	head and neck squamous cell carcinoma (HNSCC)	HNSCC patients had a significant loss in richness and diversity of microbiota species	[38]
Fusobacterium nucleatum	HNSCC	Elevated in the saliva	[39]
Corynebacterium and Kingella	HNSCC	greater oral abundance of these commensal is associated with decreased risk of HNSCC	[40]
Capnocytophaga, Pseudomonas, and Atopobium	OSCC	Highly abundant in biopsy tissue	[41]
Lautropia, Staphylococcus, and Propionibacterium	fibroepithelial polyp	Highly abundant in biopsis tissue	[41]
Treponema denticola, Streptococcus mitis, and Streptococcus anginosus	Esophageal cancer	Induction of inflammatory cytokines	[42]
Group G streptococci	Colon Cancer	Large amount of pericardial effusion	[43]
Fusobacterium nucleatum	colorectal carcinoma	Over-representation in tumor specimen	[44]

Neisseria elongate, Streptococcus mitis and *Granulicatella adiacen*	pancreatic cancer and chronic pancreatitis	Salivary microbiota as an informative source for discovering non-invasive biomarkers of systemic diseases	[45]
Helicobacter pylori	dysplasia or gastric cancer	Presence of *H. pylori* at baseline was associated with an increased risk of progression to dysplasia or gastric cancer	[46]

Similarly, the short-chain fatty acids (SCFAs) like propionate, butyrate and acetate have been found to be another biomarker for multiple sclerosis pathogenesis. Upon comparing the serum SCFAs levels of multiple sclerosis patients with healthy ones for the immune cell abundance and phenotype as well as with other relevant serum factors, a significant reduction in propionate levels in the serum of patients has been noticed. There is a positive correlation between serum propionate and the frequencies of circulating T follicular regulatory cells and T follicular helper cells. However, butyrate level is associated positively with the frequencies of IL-10-producing B-cells and negatively with frequencies of class-switched memory B-cells. In addition, acetate level is negatively correlated with TNF production by polyclonally activated B-cells. Therefore, serum SCFAs level can be associated with changes in circulating immune cells and biomarkers implicated in the development of multiple sclerosis [47]. Nevertheless, propionate and acetate produced by Propionibacterium during fermentation process is a major cytotoxic component secreted by the bacteria. SCFAs can kill human colorectal carcinoma cell lines by targeting multipal ways including apoptosis, a loss of mitochondrial transmembrane potential, the generation of reactive oxygen species, caspase-3 processing, influencing extracellular pH, and nuclear chromatin condensation, necrosis. These results suggest that SCFAs produced by propionibacteria could constitute deleterious effects to cancerous cells and constitute probiotics properties which are efficient in digestive cancer prophylaxis [48].

Due to the availability of advanced techniques like fluorescent oligonucleotide hybridization, now it's been easier to figure out the microbiome composition by labelling bacterial cells, which can be easily and readily analyzed by flow cytometry [49] and molecular-phylogenetic methods [50]. The probes labeled with tetramethylrhodamine are being used to complement short sequence elements common to phylogenetically coherent assemblages of microorganisms within the 16S rRNA and hybridized to suspensions of fixed cells. Similarly, molecular-phylogenetic methods also help to identify microbes by taking the advantage of polymerase chain reaction amplification and phylogenetic analysis of small-subunit ribosomal RNA gene sequences. This technique also helps to design sequence-based tools for identifying, tracking, and diagnosing the presence of microbes in complex samples [50].

Amplicon sequencing of the bacterial 16S rRNA gene method has been used to discriminate between pancreatic cancer patients and controls where fourteen bacterial features were found to alter [51]. Bacterial 16S rDNA Illumina® sequencing and 16S rDNA quantitative polymerase chain reaction methods help to determine the association between urinary microbiome and prostate cancer. These methodologies had been used in a study by Shrestha et al, 2018 to describe the association of prevalence of pro-inflammatory bacteria and uropathogens in the urinary tract of men with prostate cancer, that is related to the chronic inflammation condition [52].

Cancer patients suffering from renal cell carcinoma (RCC) and non-small-cell lung cancer (NSCLC) treated with anti-programmed cell death ligand-1 (PD-L1) or PD-L1 plus CTLA-4 mAb monotherapy, who were also undergoing treatment of antibiotics (β-lactam or quinolones for pneumonia or urinary tract infections) in the beginning for thirty days were examined for gut microbiota diversity and composition leading to dysbiosis. In this study, results suggested those patients' getting antibiotics suffered increased risk of primary progressive disease, which means antibiotics were affecting or lowering the effectiveness of immune-checkpoint inhibitor therapy. Antibiotics treatment increased risk of primary progressive disease in both types of cancer patients, suggesting antibiotics reduced clinical benefit from immune-checkpoint inhibitor therapy in RCC and NSCLC patients that can be modulated by altering the gut microbiota composition [53]. This fact can be seen in a study where ablation of the microbiome with immunogenic reprogramming

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protected against preinvasive and invasive pancreatic ductal adenocarcinoma (PDA). Removal of the microbiome resulted in reduction of the myeloid-derived suppressor cells and an increased M1 macrophage and T cells differentiation and activation. This strategy enabled efficacy for checkpoint-targeted immunotherapy by upregulating PD-1 expression via activating Toll-like receptors in monocytic cells [54].

Even though anticancer drug alters the intestinal microbiota in such a way causing induction of immune responses for example, Cyclophosphamide imposes antitumor immune responses by altering the composition of small intestine microbiota and induces the translocation of selected species of Gram-positive bacteria (*Lactobacillus johnsonii*, *Lactobacillus murinus* and *Enterococcus hirae*) into secondary lymphoid organs in a mouse model. These bacteria help to induce generation of pathogen specific T helper 17 (Th17) cells and memory immune responses. This fact was demonstrated by Viaud et al., where authors have shown how tumor-bearing mice treated with antibiotics got rid of Gram-positive bacteria causing reduction in pathogen specific Th17 responses that made them resistant to cyclophosphamide. Seven days post cyclophosphamide treatment, there was significant reduction in the frequencies of $CD103^+CD11b^+$ dendritic cells and $TCR\alpha\beta^+CD3^+$ T cells that were expressing the transcription factor RORγt in the lamina propria (LP) of the small intestine. However, adoptive transfer of pathogen specific Th17 cells to vancomycin-treated mice had partially restored the antitumor efficacy of cyclophosphamide suggesting the impact of gut microbiome to strengthen anticancer immune response [55].

Intact gut microbiome is required to get favorable patient outcomes during cancer chemotherapies because microbiota have direct influence on local and systemic inflammation and decide disease progression, and treatment. It has been reported that disruption of the microbiota impairs the response of subcutaneous tumors to CpG-oligonucleotide immunotherapy and platinum chemotherapy. This aspect can be seen in detail study by Iida et al., where C57Bl/6 mice had been pretreated with antibiotics cocktail containing vancomycin, imipenem, and neomycin before the tumor inoculation and continued till the end of the study conducted. Treatment of antibiotics mix reduced the frequency of monocyte derived $Ly6C^+$ MHC class II^+ cells and $Ly6G^{high}$ neutrophils. Authors observed that the production of cytokine and tumor necrosis after CpG-oligonucleotide treatment was lower in antibiotics-treated or germ-free mice suggesting the optimal response to chemotherapy demands an effective and intact gut microbiome [56]. In a study T cell infiltration to solid tumors facilitated immunotherapy. Immune cells infiltration to the tumor site makes immunotherapies to work as described by Sivan et al., by using 16S ribosomal RNA sequencing method to identify functionally relevant bacteria taxa. Comparative analysis between high rate growing tumor bearing mice from Jackson Laboratory and slow growing tumor bearing mice from Taconic Farms revealed 257 taxa were significantly different. Further analysis identified *Bifidobacterium* association with the antitumor effects since its combined treatment with PD-L1-specific antibody therapy abolished tumor outgrowth. This resulted in accumulation of antigen-specific T cells and induced IFN-γ by enhancing the dendritic cell function leading to enhanced $CD8^+$ T cell priming and accumulation in the tumor microenvironment [57].

Research had shown how disrupting the β-glucuronidase enzymes activity, which is present in the commensal microbiota can alleviate the toxicity caused after using anticancer drugs. There was a study focused not to alter the bacterial population but to target symbiotic bacterial β-glucuronidases causing severe diarrhea upon colon cancer chemotherapeutic CPT-11 (irinotecan) treatment. CPT-11 is a derivative of known potent antineoplastic compound Camptothecin, which is under clinical use but still elicits pronounced side effects that limit its efficacy. Authors screened bacterial β-glucuronidase inhibitors by high-throughput screening using a β-glucuronidase assay. This investigation selected potential inhibitors, which had no effect on the orthologous mammalian enzyme since crystallographic studies revealed that, *E. coli* enzyme contains a 17-residue "bacterial loop", which is not present in the human ortholog, that makes it selective to bacterial enzyme not to mammalian enzymes. Findings were confirmed in mice showing oral administration of a β-glucuronidase inhibitor protected Balb/cJ mice from CPT-11–induced toxicity without losing the glandular structures of the intestinal tissues and keeping the intact gastrointestinal epithelium and

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thereby reduced both diarrhea and bloody diarrhea. Therefore, drugs should be designed to inhibit undesirable enzyme activities rather than alter the actual microbiome to enhance chemotherapeutic efficacy [58].

4. Probiotics improve cancer treatment

There are diverse procedures these days to go with surgery such as chemotherapy, radiotherapy, immunotherapy and hormonal therapy that produce a lot of side effects especially abdominal pain, severe gastric issues, constipations, nausea, vomiting, diarrhea, taste disturbances, mucositis, and swallowing difficulties quality of life of these patients [1,59]. Thanks to advanced research therapeutic strategies that started using probiotics to modify microbiota to manage these complications (Table 2). Number of studies have proposed and confirmed that probiotics can be effective at controlling growth of cancer cells [1,60–63].

Table 2. Probiotics to support cancer treatment.

Probiotics	Cancer type	Study model	Effect	Ref.
Propionibacterium freudenreichii	Colorectal cancer	HT-29 cells	Induced cell cycle arrest in the G2/M phase	[64]
Enterococcus faecium RM11, Lactobacillus *fermentum* RM28	colon cancer	Caco-2 cells	Triggered antiproliferation of colon cancer cells	[65]
Yogurt probiotics	Colorectal cancer	Clinical trial		[66]
Lactobacillus plantarum AS1	colon cancer	rat	Antioxidant-dependent mechanism	[67]
Lactobacillus casei and *Lactobacillus rhamnosus* GG	Colorectal cancer	HCT-116 cells	Decreased metalloproteinase-9 activity and increase the levels of tight junction protein zona occludens-1	[68]
Lactobacillus plantarum AS1	Colorectal Cancer	Male Wistar Rats	Antioxidant property reduced tumor volume diameter and total number of tumors	[69]
Lactobacillus acidophilus	Breast cancer	Balb/C inbred female mice	Induces production of IFNγ, IL-4 and TGF-β	[70]
L. casei Shirota	Breast cancer	case-control study	NK cell activation and NK cell mediated antitumor activity	[71]
Lactobacillus casei Shirota	Breast cancer	population-based case-control Study	Enhanced NK cell activity mediated antitumor activity	[72]
Lactobacillus fermentum	Colorectal cancer	Caco-2 colon cancer cell	Antiproliferative activity	[73]
Dead nano-sized Lactobacillus *plantarum*	Colon Cancer	Balb/c mice	Suppressed inflammation, induced cell cycle arrest and apoptosis, and enhanced IgA secretion	[74]
Lactobacillus lactis NK34	Lung, colon, gastric adenocarcinoma, breast cancer	SK-MES-1, DLD-1, HT-29, LoVo, AGS, and MCF-7 cells, RAW 264.7 cells	Reduced production of nitric oxide and proinflammatory cytokines (tumor necrosis factor-α, interleukin-18, and cyclooxygenase-2)	[75]
Lactobacillus casei ATCC334	colon cancer	Human colon cancer cell lines (Caco2$_{bbe}$, SKCO-1 and SW620) and Xenografts (SW620 cells injected into male BALB/c nude mice)	Ferrichrome induced apoptosis by activating C-jun N-terminal kinase and suppressed tumour growth	[76]

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Lactobacillus casei ATCC 393	colon cancer	murine (CT26) and human (HT29) colon carcinoma cell lines	Apoptotic Cell Death and upegulation of TRAIL in colon carcinoma cells	[77]
Lactobacillus casei BL23	Colitis-Associated Colorectal Cancer	C57BL6 mice	Immunomodulatory effect, mediated through the downregulation of the IL-22 cytokine, and an antiproliferative effect, mediated through the upregulation of caspase-7, caspase-9, and Bik	[78]
Lactobacillus acidophilus ATCC 314 and *Lactobacillus fermentum* NCIMB 5221	Colorectal cancer	Apc $^{Min/+}$ CRC mouse	Down-regulated proliferation markers (Ki-67, E-cadherin, β-catenin)	[79]
Lactobacillus reuteri NCIMB 701,359	Colorectal cancer	DLD-1 cell line	Probiotic-derived protein, p8 inhibit p53-p21-Cyclin B1/Cdk1 signal pathway	[80]
Acetobacter syzygii	squamous cell carcinoma	Human oral cancer (KB) and human normal epithelial (KDR) cell lines	Induced apoptosis	[81]
Bifidobacterium longum, Collinsella aerofaciens, and *Enterococcus faecium*	metastatic melanoma	melanoma patients	Enhanced systemic and anti-tumor immune responses mediated by increased antigen presentation, and improved effector T cell function	[82]
Akkermansia muciniphila	non-small cell lung cancer, renal cell cancer, and urothelial cancer	Mice	increasing the recruitment of CCR9+CXCR3+CD4+ T lymphocytes	[83]
Lactobacillus acidophilus 20079	colon cancer	colon cancer (CaCo-2) and Human breast cancer (MCF7) cell lines	Increased apoptosis in in sub-G0/G1 cell cycle phase, stimulate immune response and inactivate NF-κB inflammatory pathway	[84]
Recombinant *Lactococcus lactis*		mouse allograft model of human papilloma virus (HPV)-induced cancer, and TC-1 Cell Line	Secreting IL-17 to stimulate the TH17 pathway	[85]
Streptococcus thermophilus	Colorectal cancer	HT-29 human colorectal adenocarcinoma cells	High production of folic acid, tyramine and histamine, high cytotoxic to cancer cells	[86]
Bifidobacterium breve lw01	Head and neck cancer	SCC15, CAL 27 and WSU-HN6 cell lines	Increased expression of cell apoptosis protein caspase 3, PARP and the proportion of Cl-PARP/PARP	[87]
Lactobacillus and Bifidobacteria strain	CRC	randomized double-blind placebo- controlled trial	Interfere with the signalling pathways to stimulate or suppressor the level of cytokines production	[88]
Enterococcus faecalis	Colorectal Cancer	C57BL/6 mice	Inhibit NLRP3 inflammasome activation in macrophages	[89]
Lactobacillus delbrueckii ssp. bulgaricus B3	colon cancer	HT-29 cells	Inhibit cell proliferation in HT-29 via apoptosis	[90]
Recombinant Lactococcus lactis	Colorectal cancer	murine fibroblasts 3T3 L1 cells line and mouse allograft model of human	Efficiently secretes biologically active IL-17A cytokine	[91]

		papilloma virus-induced cancer		
Lactobacilli cocktail	colorectal cancer	HT-29 colon carcinoma cells	Anti-tumor effects on HT-29 cells by modulating the Notch and Wnt/β-catenin pathways	[92]
Lactobacillus reuteri	Colon Cancer	Colon Cancer Stem-Like Cells (HT29-ShE)	anti-metastatic and anti-proliferative	[93]
Kluyveromyces marxianus and *Pichia kudriavzevii*	colon cancer	colon cancer cell lines (SW-480, HT-29, HCT-116)	Hinder AKT-1, mTOR, and JAK-1 pathways, and induce apoptosis	[94]

Intake of fermented dairy products reduces the risk of cancer by inducing immune responses and creating balanced and healthy gut microbiomes to support all therapies. A detailed long study conducted for 12 years to determine the effect of yogurt consumption on cancer prevention in volunteers of the EPIC-Italy cohort suggested the protective role of yogurt against colorectal cancer (CRC). This finding suggested that yogurt should be part of a diet to prevent the disease [95].

Exopolysaccharides derived from probiotic yeast *Kluyveromyces marxianus* and *Pichia kudriavzevii* have shown inhibitory effect on different colon cancer cell lines hindering AKT-1, mTOR, and JAK-1 pathways, and induce apoptosis [96]. Patients receiving CRC undergoing perioperative probiotic administration of combined probiotics containing *Bifidobacterium longum* (≥ $1.0*10^7$ cfu/g), *Lactobacillus acidophilus* (≥ $1.0*10^7$ cfu/g), and *Enterococcus* faecalis (≥ $1.0*10^7$ cfu/g) significantly influenced the recovery of bowel function [97].

One of the most widely used probiotic strains is Lactobacillus, lactic acid-producing bacteria which continuously being studied and used to improve function of the gut system. In this context, a study tested *Lactobacillus reuteri* FLRE5K1 for its anti-melanoma activity in cell assays and animal models. Results showed that treatment with *Lactobacillus reuteri* FLRE5K1 reduced the incidence of tumor as compared to the model group. FLRE5K1 didn't inhibit the melanoma tumor mass but prolonged the survival of tumor-bearing mice. Uptake of *Lactobacillus reuteri* FLRE5K1 by immune cells induced the levels of TNF-α and INF-γ in serum suggesting the stimulation of immune responses and limited the infiltration of melanoma cells with blood circulation [98]. In addition to prolonging the survival of tumor bearing mice, *Lactobacillus reuteri* helps in alleviating liver injury and intestinal inflammation induced by D-galactosamine in Sprague–Dawley (SD) rats. Probiotics works through maintaining the redox homeostasis by increasing the expression of intestinal tight junction protein proteins ZO-1 and occludin that facilitated the intestinal barrier morphology to remain intact. Supplementation of *Lactobacillus reuteri* inhibited intestinal apoptosis by downregulating the expression of caspase-3 and activated Nrf-2 nuclear translocation and elevated induction of HO-1 via activating phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), protein kinase C (PKC), and their phosphorylated forms [99]. Treatment with anti-cytotoxic-T-lymphocyte-associated protein 4 (CTLA-4) or PD-1/PD-L1 triggers severe inflammatory side effects such as colitis due to change in the composition of the gut microbiota especially reduction in the abundance of Lactobacillus. In this case as well oral administration of *Lactobacillus reuteri* inhibited the development and progression of colitis by restoring the colon structure and less leukocyte infiltration. Its treatment decreased the inflammatory cytokines (KC, TNF-α, IFN-γ, and IL-6) and rescued the loss of body weight and inflammatory status induced by anti-CTLA-4 or anti-PD-L1 immunotherapy [100].

Another example *Lactobacillus rhamnosus* GG showed protective benefits against colon by suppressing proliferation and promoting apoptosis in colon cancer cell lines [60]. Consequently, administration of a probiotic combination could indeed restore immune function and restore the composition of altered gut microbiota. Consumption of yogurt containing high counts of viable *Streptoccocus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* was inversely associated with risk of colorectal cancer by lowering the levels of cancer biomarkers, stimulating the anticancer effect and increasing the survival rate [66]. Similarly, in a double-blind trial conducted with 138 patients suffering with superficial transitional cell carcinoma of bladder showed better prophylactic effect of

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consuming *Lactobacillus casei* preparation [101]. *Lactobacillus casei* BL23 treatment in C57BL6 mice protected against colitis-associated colorectal cancer by inducing immunomodulatory effect upon downregulating IL-22 cytokine and inducing antiproliferative effect through upregulating *caspase-7, caspase-9*, and *Bik* RNA expression and downregulating Ki67 levels [78]. Nonetheless, this strain induces IL-17A, a pro-inflammatory cytokine production by TH17 cells participates in antitumor effects. In this study Jacoutan et al., has developed recombinant strain of *Lactobacillus casei* BL23 capable of secreting IL17A to understand the involvement of IL17A in cancer. Their results showed that around 26% of mice treated intranasally with *L. lactis*-IL-17A and challenged with tumor cell line, TC-1 cells derived from lung epithelial cells of C57BL/6 mice remained protective against tumor confirming the anti-tumor effect of IL17 cytokine by inducing IL-6 secretion in splenocytes [91]. Another population-based case control study based on questionnaire and interview was conducted to test the combination effect of regular consumption of *Lactobacillus casei* Shirota (BLS) and isoflavones association with the incidence of breast cancer in Japanese women, where 306 cases with breast cancer and 662 controls aged 40-55 included in the analyses. Their analysis suggested the inverse association between soy consumption and breast cancer incidence could be due to isoflavones anticancer properties and inducing natural killer cells activity [71].

Moreover, *Streptococcus thermophilus,* a lactic acid bacterium known to be used as starter culture for a number of dairy products to produce folate during growth. Its cytotoxic effect on cancer cells was tested in a study using eight *S. thermophilus* strains (1F8CT, MTH17CL396, M17PTZA496, TH982, TH985, TH1435, TH1436, TH1477) isolated from curd, cheese, whey and raw milk dairy products in Italy [102]. This group has evaluated all the strains for number of health-related traits such as production of folic acid and anticancer property by evaluating the ability to attach and inhibit the growth of human HT-29 colorectal adenocarcinoma cells. Results revealed that two strains of *S. thermophilus* strains, namely M17PTZA496 and TH982 have probiotic properties along with anticancer activity along and folate production capability. These strains were superior to *Lactobacillus rhamnosus* GG for some of these properties that suggest they can pose better health benefits if used commercially but before that they need to be studied in more detail.

In addition to probiotics, prebiotics can also manage gut microbiota and alleviate side effects of cancer therapies and prevent gastric cancer. Prebiotics promote growth of beneficial bacteria and possess protective effects against colon carcinogenesis. Fermentation of prebiotics by gut microflora generates short chain fatty acids that alter the gene-expressions and differentiation of tumor cells [103]. *In vivo* study on azoxymethane/dextran-sodium-sulfate-induced colorectal cancer in C57BL/6 mice has shown prebiotics preventive effect against colorectal cancer [104]. A clinical trial on colorectal cancer patients showed that preoperative oral supplementation can alleviate post-operative complications. Patients received daily oral intake of 30 g prebiotic supplement showed positive effects on immune status [105]. Not only does intake of prebiotics prevent cancer but also increases prevalence of commensal microbiota (*Bacteroides, Bifidobacterium, Escherichia-Shigella*, and *Enterococcus*) in these individuals. Another randomized double-blind trial conducted on 73 colorectal cancer patients with preceding colorectal operations when treated with oral intake of higher concentrations of lactic acid bacteria had not shown severe inflammatory response after surgery [106].

Gut microbiome impacts the therapeutic outcome for checkpoint blockade immunotherapy in human cancer patients. Examination of the oral and gut microbiome of melanoma patients under the treatment of anti-PD-1 immunotherapy demonstrated a significant difference in the diversity and composition of gut microbiome. Patients' fecal samples showing high diversity and abundance of *Ruminococcaceae/Faecalibacterium* had significantly better progression-free survival. These changes in gut microbiome may modulate the therapy response to anti-PD-1 in melanoma patients by modulating the immune response. Patients with higher abundance of these strains resulted with higher levels of CD4+ and CD8+ T cells in the systemic circulation [82]. In line with this, T cell responses during immunotherapies depend on distinct Bacteroides species, *Bacteroides thetaiotaomicron* or *Bacteroides fragilis.* CTLA blockade effect on tumors was not enough in mice treated with antibiotic-treated or germ-free, while the defect was overcome by adoptive transfer of *B. fragilis-*

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specific T cells [107]. A study applied combination of eleven bacterial strains (*Parabacteroides distasonis, Parabacteroides gordonii, Parabacteroides johnsonii, Alistipes senegalensis JC50, Paraprevotella xylaniphila, Bacteroides uniformis, Bacteroides vulgatus, Eubacterium limosum, Ruthenibacterium lactatiformans strain 585-1, Phascolarctobacterium succinatutens YIT 12067, Fusobacterium ulceranus*) from healthy human donor feces to syngeneic tumor mice models. All the strains altogether mediate the local and systemic immunomodulation by enhancing the recruitment of IFNγ^+ CD8 T cells in the intestine without causing inflammation due to CD103$^+$ dendritic cells and major histocompatibility (MHC) class Ia molecule. This strain mixture has not only enhanced the host resistance against *Listeria monocytogenes* infection but also improved anti-cancer immunity in tumor models [108]. Similarly, fecal transplantation therapy by low volume enema helped to overcome the side effects raised from chronic antibiotic (oral vancomycin) therapy [109]. Treatment with antibiotics ameliorates the benefits of immune checkpoint inhibitors. Administration of fecal microbiota from cancer patients who responded to immune checkpoint inhibitors helped to reverse gut microbiota dysbiosis to a healthy gut environment in mice models. These patients' stool was highly abundant of *Akkermansia muciniphila,* therefore its oral supplementation restored the efficacy of PD-1 blockade. Adjuvant effect of *A. muciniphila* induced dendritic cells to secrete IL-12, a Th1 cytokine having importance in immunogenicity of PD-1 blockade in eubiotic conditions helped to recruit CCR9+CXCR3+CD4+ T lymphocytes into mouse tumor beds within 48 hours after the first injection in mesenteric lymph nodes [83].

Enterococcus faecium RM11 and *Lactobacillus fermentum* RM28 isolated from fermented dairy milks trigger antiproliferation of colon cancer cells at the rates of 21–29%, and 22–29% respectively [110]. Colorectal cancer patients treated for six months with probiotic containing 30 X 10^9 colony-forming unit mixture of six Lactobacillus and Bifidobacteria strains showed significant reduction in the level of pro-inflammatory cytokine, TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-17C and IL-22 and also avoid the requirement of antibiotics and showed no infections [88].

Collectively, all these studies suggest any change or dysbiosis in gut microbiota have a significant effect on cancer growth, development, and its treatment [111,112]. The challenges faced during cancer therapies i.e., chemotherapy, surgery, immunotherapy, and radiotherapy mainly include diarrhea, mucositis, abdominal pain, and quality of life or the adverse effects caused by heavy antibiotics treatment can be alleviated by encouraging alternative therapeutic methods along with cancer therapies involving adjuvant therapies like application of probiotics in the clinical management. Including probiotics, synbiotics or probiotics in a correct manner can help to resolve these cons (Table 3). Administration of yeast probiotics has been shown to have an adjuvant property to treat colorectal cancer by several means including boosting immunological and antioxidant properties [113]. Antioxidant properties have greater implication on cancer treatment as can be seen in a study where *Lactobacillus plantarum* AS1 (AS1) showed its direct impact on colon cancer treatment by inducing activities of antioxidant enzymes e.g., lipid peroxide, superoxide dismutase, catalase, glutathione-S transferase, alkaline phosphatase and acid phosphatase in colon and plasma of cancer-bearing animals [67].

Table 3. Clinical trial using probiotics during cancer treatment.

Probiotics	Cancer type (year)	Effect	Ref.
Lactobacillus casei LC9018	Lung cancer (malignant pleural effusions secondary to lung cancer) (1991)	• Significantly greater improvement in performance status and symptoms (chest pain, chest discomfort, and anorexia) • Response rate for treatment with intrapleural doxorubicin plus LC9018 was significantly higher	[114]
Lactobacillus rhamnosus GG ATCC 53103	Colorectal cancer (Lactose intolerance associated with adjuvant 5-fluorouracil-based chemotherapy) (2007)	• Bowel mucosal injury associated with 5-fluorouracil (5-FU) treatment. • The frequency of severe 5-FU-based chemotherapy-related diarrhea was reduced	[115]

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Lactobacillus casei DN-114 001	Endometrial adenocarcinoma patients (2008)	• Oral supplementation does not reduce the incidence of radiation-induced diarrhea. • Showed significant effect on stool consistency	[116]
Lactobacillus acidophilus plus *Bifidobacterium bifidum*	Cervical cancer (2010)	• Reduced the incidence of radiation-induced diarrhea and the need for anti-diarrheal medication and • Significant benefit on stool consistency.	[117]
Lactobacillus rhamnosus GG	Colorectal cancer (2013)	• Lactobacillus intervention during 5-fluorouracil chemotherapy • reduced diarrhea only in nonproducers of methane.	[118]
Lactobacillus acidophilus	Prostate cancer (2013)	• Useful in reducing the percentage volume change of the rectum, crucial factor of prostate movement	[119]
Bifidobacterium, Lactobacillus and *Streptococcus thermophilus*	Acute radiation enteritis (2014)	• Treated group showed better food intake than control group	[120]
Lactobacillus acidophilus, *Lactobacillus rhamnosus*, *Lactobacillus casei* DN-114001 and *Bifidobacterium bifidum*	Abdominal or pelvic cancer (2014)	• Beneficial effects on treatment of radiation-induced diarrhea • and improve the quality of patients' lives.	[121]
Lactobacillus acidophilus BMC12130, *Lactobacillus casei* BCMC12313, *Lactobacillus lactis* BCMC12451, *Bifidobacterium bifidum* BCMC02290, *Bifidobacterium longum* BCMC02120 and *Bifidobacterium infantis* BCMC02129	Colorectal cancer (2017)	• Improve quality of life • Reduce certain inflammatory biomarkers (IL-6) and relieve certain side effects of chemotherapy	[122]
Bifidobacterium breve strain Yakult, *Lactobacillus casei* strain Shirota	Esophageal cancer (2017)	• Reduced the occurrence of adverse events of chemotherapy through adjustments to the intestinal microbiota. • Concentrations of acetic acid and propionic acid were significantly higher in the synbiotics group. • The frequencies of severe lymphopenia and diarrhea were significantly less. Febrile neutropenia occurred less in the synbiotics group.	[123]
Lactobacillus acidophilus LA-5 plus *Bifidobacterium animalis* subsp. *lactis* BB-12	Cervical cancer (2019)	• Incidence of diarrhea was reduced. • Severity of abdominal pain was significantly reduced	[124]
Lactobacillus brevis CD2	Head and neck cancer (2019)	• Modulated homeostasis of the salivary microbiota	[125]
Bifidobacterium longum, *Lactobacillus lactis* and *Enterococcus faecium*	Nasopharyngeal carcinoma (2019)	• Significantly increased the Immune responses, • Reduced the severity of oropharyngeal mucositis	[126]
Lactobacillus acidophilus, *Lactobacillus casei*, *Lactobacillus plantarum*,	Colorectal cancer (2019)	• Significant reduction in postoperative complications in the localization of tumours on	[127]

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Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium breve, Streptococcus thermophilus		the rectum -33.3% and the ascending colon -16.7%.	
Streptococcus salivarius M18	Head and neck cancer (2020)	• Improvement in periodontal screening and plaque index scores was observed.	[128]
Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum and *Saccharomyces boulardii*	Head and neck cancer (2020)	• Significant reduction in Candida spp. counts specifically significant decrease in Candida glabrata and Candida tropicalis	[129]
Lactobacillus plantarum MH-301 (CGMCC NO. 18618), *L. rhamnosus* LGG-18 (CGMCC NO. 14007), *Lactobacillus acidophilus and Bifidobacterium animalis subsp.lactis* LPL-RH (CGMCC NO. 4599)	Gastric cancer (2021)	• Probiotic compounds can restore gut microbiota homeostasis, reduce inflammation, maintain intestinal mucosal barrier and immunity, finally promote recovery after gastrectomy	[130]
Bifidobacterium longum, Lactobacillus acidophilus and Enterococcus faecalis	Breast cancer (2022)	• Probiotic supplement attenuates chemotherapy-related cognitive impairment in patients.	[131]
Bifidobacterium infantis, Lactobacillus acidophilus, Enterococcus faecalis, and Bacillus cereus	Thyroid cancer (2022)	• Probiotics alleviated lack of energy, constipation, weight gain, and dry mouth and decreased the levels of fecal/serum LPS and plasma lipid indicators (total cholesterol, triglycerides, low-density lipoprotein, and apolipoprotein A).	[132]
Lacticaseibacillus paracasei strain Shirota (YIT9029), Bifidobacterium breve strain Yakult,	Esophageal cancer (2022)	• Incidences of grade 4 neutropenia and grades 2–4 diarrhea was significantly reduced	[133]
Bifidobacterium infantis, L. acidophilus, Enterococcus faecalis, and Bacillus cereus	Colorectal Cancer (2023)	• Reduce chemotherapy-induced gastrointestinal complications, especially in the case of diarrhea. • Probiotics also promote the production of short-chain fatty acids, particularly increasing acetate, butyrate, and propionate.	[134]

5. Conclusion

Taken together this article highlighted upon the quality and type of food to be consumed and not to consume, which can enhance the risk of cancer. Disturbance in gut microbiome led to resistance to cancer therapies and ameliorated its beneficial effects. Gut microbiota helps immune response to support immunotherapies by using probiotics and prebiotics as an adjuvant. Several clinical trials and *in vivo*, *in vitro* experiments have proposed on the usage of these adjuvant therapies, which can shape the intestinal microbiota that is disturbed in diseased condition and helps to promote the overall wellness. In this review, we focused on the identification of microbiome as a biomarker of diseased condition and how specific usage of probiotics, or some strains can be useful to improve the efficacy of treatment and eliminate the side effects.

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