J Appl Biotechnol Rep. 2023 December;10(4):1123-1139

Journal of
Applied Biotechnology Reports

doi 10.30491/JABR.2023.401696.1644

Review Article

The Anticancer Properties of Probiotic Species

Mansoor Khaledi [1], Hadi Esmaeili Gouvarchin Ghaleh [2], Mohammad Ali Abyazi [1], Hamideh Mahmoodzadeh Hosseini [3], Reza Golmohammadi [1*]

[1] Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Applied Virology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3] Applied Microbiology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

Corresponding Author: Reza Golmohammadi, PhD, Assistant Professor, Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL), Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran. Tel: +98-9126135476, E-mail: rsr.golmohammadi@bmsu.ac.ir, Golmohammadi27@gmail.com

Received June 11, 2023; **Accepted** October 24, 2023; **Online Published** December 6, 2023

Abstract
The maintenance of homeostasis can be influenced by the gut microbiota. An imbalance in the gut microbiota, known as gut microbiota dysbiosis, can result in the deterioration of the mucosal layer and the integrity of the intestinal epithelial barrier. Consequently, this can lead to the infiltration of bacteria into the lamina propria. The disruption in the gut microbiota balance can also trigger innate immune responses, causing inflammation. Consequently, this inflammation has the potential to initiate various types of cancers. Numerous studies have indicated that probiotics play a direct or indirect role in regulating immune responses by modulating the gut microbiota. Hence, they can be employed as a preventive measure against cancer. This review aims to explore the potential of probiotics in countering cancer metastasis and inhibiting the proliferation of cancer cells in different types of cancer including hepatocellular carcinoma, colorectal cancer, gastric cancer, esophageal cancer, breast cancer, bladder cancer, and cervical cancer.

Keywords: Cancer, Carcinoma, Gut Microbiota, Probiotic, Anticancer
Citation: Khaledi M, Esmaeili Gouvarchin Ghaleh H, Ranjbari N, Abyazi MA, Mahmoodzadeh Hosseini H, Golmohammadi R. The Anticancer Properties of Probiotic Species. J Appl Biotechnol Rep. 2023;10(4):1123-39. doi:10.30491/JABR.2023.401696.1644

Introduction

In the field of tumor research, William Cooley was the first to demonstrate the antitumor effects of a combination of microbial products, specifically *Streptococcus pyogenes* and *Serratia marcescens*.[1] The gut microbiota represents an ecological system consisting of various commensal microorganisms that metabolize residual food, intestinal secretions, and digestive juices, and shed colonocytes. In the large intestine, proteolytic fermentation increases with a high intake of dietary protein, resulting in the production of substances such as phenolic compounds, amines, ammonia, N-nitroso compounds, and indoles. These compounds can exert carcinogenic effects on the differentiation and proliferation of epithelial cells.[2,3] The microbiota also influences the expression of numerous human genes. For instance, specific strains of Bifidobacteria, Lactobacillus, and *Escherichia coli* can impact mucin gene expression, toll-like receptor (TLR) signaling in dendritic cells and macrophages, as well as caspase expression, thereby modulating immune activity and apoptosis. The interaction between commensal bacteria and immune cells establishes a balance between proinflammatory genes, proto-oncogenes, anti-inflammatory genes, and tumor suppressor genes.[3-5] An imbalance in the intestinal microbiota disrupts the normal functioning of bacteria, leading to an attack on the intestinal lining and surrounding tissues, resulting in inflammation.[6] This inflammatory process plays a significant role in promoting tumor growth, facilitating the invasion of tumor cells, and eventually leading to metastasis. Certain inflammatory cytokines have the ability to directly damage the DNA of epithelial cells, contributing to the development of inflammation-related cancers.[7] The exposure to carcinogens and other cancer-causing molecules is a crucial factor in cancer development. For instance, diet can impact the diversity of the gut microbiome. That the consumption of high-fat diets among healthy young individuals can lead to unfavorable changes in the intestinal microbiota. Moreover, certain types of bacteria have been associated with tumor formation under specific conditions. Alterations in the intestinal microbiota, through various pathways, can influence susceptibility to different types of cancer. Furthermore, bacteria and their metabolites not only contribute to the development of cancer but can also impact the therapeutic efficacy of anticancer drugs (Figure 1).[8-11] The intestinal microbiota also has an impact on the side effects associated

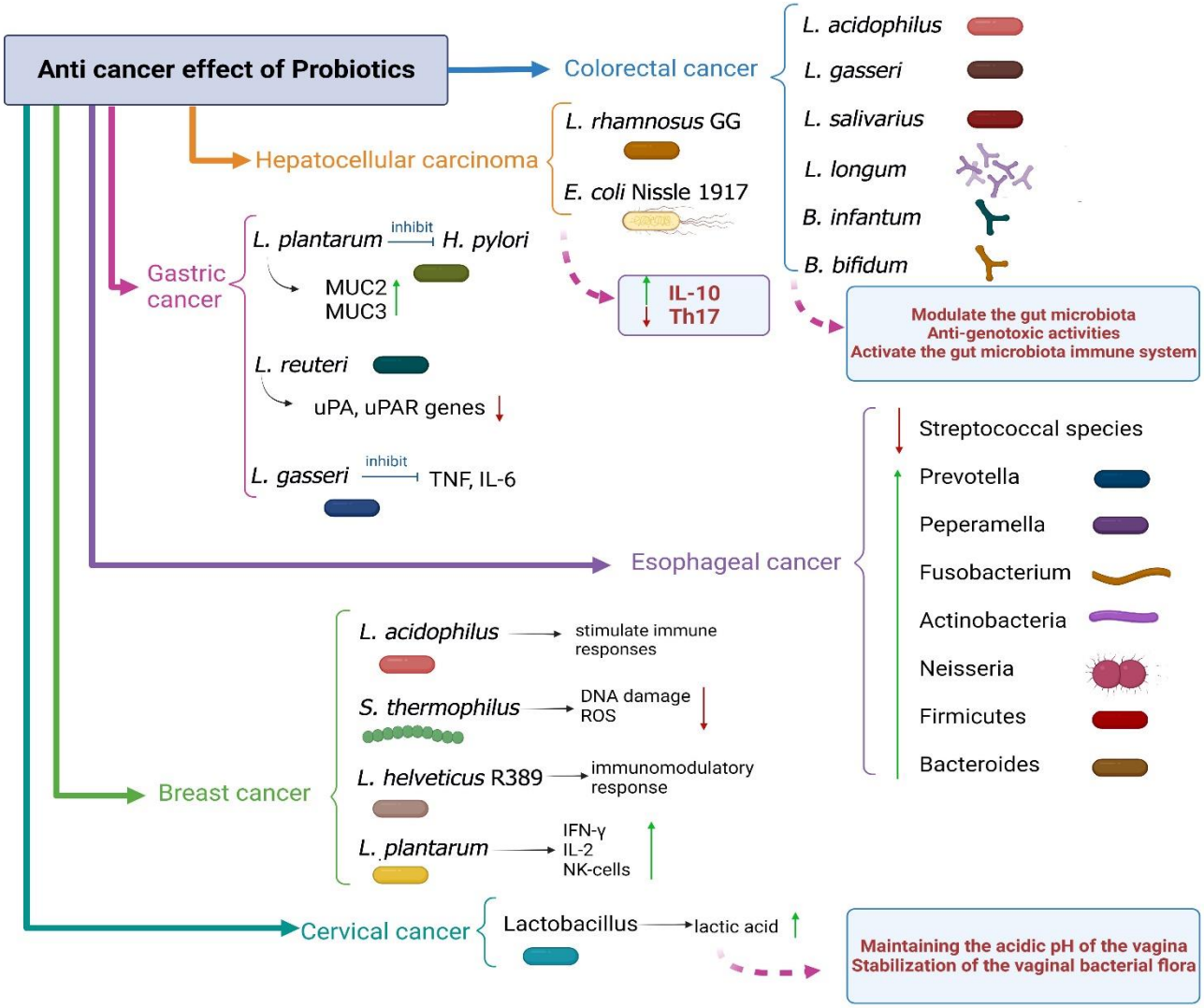

Figure 1. Anticancer Activity of Probiotics in Various Cancers.

with cancer treatments. For example, chemotherapy can lead to damage to the mucosal layer and the integrity of the intestinal epithelial barrier, allowing bacteria to penetrate into the lamina propria. The transfer of these bacteria can activate the innate immune system, triggering inflammation. This inflammation not only influences cancer progression but also affects the response to cancer treatments such as chemotherapy, radiotherapy, and immunotherapy. Modulating the gut microbiota represents a novel approach to optimize individual responses to cancer treatments and reduce the susceptibility to toxic side effects.[12] Cancer is a leading cause of death in societies, and its development involves a combination of various factors, including chemical, radiation, viral, and genetic influences.[13] Any intervention that involves the removal, inhibition, or inactivation of mutational substances associated with cancer is highly valuable.[14] It is noteworthy that cancer ranks as the first and second leading cause of death in developed and developing countries, respectively.[15] Among the prevalent types of cancer worldwide, colon cancer holds significant importance. Colorectal cancer, which includes colon cancer, is the third most commonly diagnosed cancer in both men and women. Approximately 75% of patients with colorectal cancer have sporadic forms of the disease.[16] Another noteworthy type of cancer is hepatocellular carcinoma (HCC), which represents one of the most common and perilous forms of liver cancer. HCC ranks as the fifth most common cancer globally and stands as the second leading cause of death from tumors worldwide.[17,18] Gastric cancer is another prevalent and highly dangerous type of cancer. In terms of incidence, stomach cancer ranked as the fifth most common type of cancer diagnosed in 2018. It also accounted for 8.2% of all cancer-related deaths in 2018, making it the third leading cause of cancer-related mortality after lung cancer (18.4%) and colorectal cancer (9.2%).[19,20] The side effects of drugs, time-consuming, expensive, and complete ineffectiveness of these treatment methods justify the need to search for new methods and solutions to prevent infection. According to the

mentioned cases, it is important to provide alternative solutions for the treatment and prevention of malignancies and different types of cancers. Among the alternative solutions that are proposed for the treatment and prevention of cancer, we can mention the use of microbial products. More than 100 trillion microorganisms form a wide and diverse microbial community in the human digestive system, which are defined as intestinal microbiota.[21] Probiotics are a group of living microorganisms that, if consumed in a certain amount, create beneficial effects on the health of consumers. Lactobacillus bacteria are the most microorganisms that have been used as probiotics. Studies have shown that probiotics, including Lactobacilli, inhibit the growth of many types of pathological cells. These bacteria, which have been proposed as probiotics, increase the host's immune response and also have preventive effects on cancer and inhibit the growth of cancerous tumors.[22] The use of probiotics is considered a very positive way to treat and prevent cancers. Probiotics are living microorganisms that can be effective in host health in certain amounts.[23,24] Based on the explanations given and the importance of the topic, we decided to investigate probiotics and their anticancer effects on various cancers.

Association of Gut Microbiota and Cancer

The gut microbiota refers to the community of microorganisms that inhabit the gastrointestinal ecosystem. The gastrointestinal tract microbiota consists primarily of 10^{14} bacteria, along with various archaea, eukaryotes, and viruses.[25] This microbiota plays a crucial role in numerous essential functions, including the production of vitamins, metabolism of food components, maintenance of immune homeostasis, and acting as a biological barrier within the intestine. It also has the potential to modulate the therapeutic effects of anticancer immunomodulating agents like cyclophosphamide and may influence anticancer immunotherapy.[26-28] By reducing the systemic inflammatory index through proinflammatory cytokines and inflammatory cells, intestinal bacteria may inhibit the primary carcinogenic processes in the distal intestinal epithelium.[29] Studies have revealed that mice depleted of their gut microbiota exhibit reduced expression of genes related to inflammation and immunity in tumors, as well as a decrease in the population of inflammatory myeloid cells within the tumor microenvironment. Restoring the microbiota through oral gavage with *Alistipes shahii* reinstated tumor inflammation in microbiota-deficient mice.[30] Furthermore, it has been reported that *Faecalibacterium prausnitzii* inhibits the secretion of interleukin-6 (IL-6) and the phosphorylation of Janus kinases 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) in breast cancer cells, thereby suppressing their growth. This inhibition occurs through the IL-6/STAT3 pathway.[29] However, disruption of gut microbial communities, known as dysbiosis, can lead to various inflammatory, immune, and infectious diseases and may be associated with the development of malignancies, including lymphoma, breast cancer, colorectal cancer, and even chemotherapy-related complications.[29,31,32] Dysbiosis has the potential to increase the susceptibility to infection by opportunistic pathogens that secrete toxins capable of contributing to genomic instability, tumor initiation, and progression in susceptible cells.[33] For instance, pathogenic *E. coli* carrying pks toxicity genes have been linked to local tissue inflammation and colon carcinogenesis.[34] Recent studies have highlighted the differences in gut microbiota composition between cancer patients and healthy individuals.[35] Certain bacteria, such as colibactin-producing *E. coli*, *Bacteroides fragilis*, *Fusobacterium nucleatum*, and Providencia, have been implicated in colorectal carcinogenesis, while there is a significant decrease in butyrate-producing bacteria like Roseburia and Faecalibacterium.[36] The gut and oral microbiota of pancreatic cancer (PC) patients differ from those of healthy individuals, and the bacteria present in PC tissues are associated with patient prognosis.[30] Xenografted mouse models treated with gemcitabine have shown proinflammatory changes in the gut microbiota, with an increase in Proteobacteria and Veromicrobia and a decrease in Firmicutes and Bacteroidetes. Furthermore, the NF-kB inflammatory pathway is activated in tumor tissue.[35] Numerous studies suggest that breast cancer (BC) is associated with bacterial dysbiosis in both the intestinal microenvironment and breast tissue.[32] Interestingly, the gastrointestinal microbiome can modulate systemic estrogen levels, and gut dysbiosis has been linked to breast cancer through interactions with elevated circulating estrogen levels.[29] In terms of the relationship between gut and breast microbiota, researchers have hypothesized that the transfer of bacteria from the gut to breast tissue is a mechanism by which distinct breast tissue microbiomes associated with malignancy are established.[33] It is further hypothesized that changes in the composition and function of specific species of breast and gut bacteria may contribute to the development and progression of breast cancer through multiple pathways.[32] The immune responses of neutrophils to the gut microbiome have a significant impact on the progression of carcinogenesis in non-intestinal tissues, including mammary glands.[29] Toll-like receptor 5 (TLR5) receptors, highly expressed in breast carcinoma, can be activated by flagellin ligands, leading to strong anti-tumor activity and inhibition of breast cancer cell proliferation. Gut bacteria have the ability to upregulate Toll-like receptors (TLRs) and activate NF-κB, which plays a crucial role in regulating inflammation. TLRs are involved in the initiation and promotion of breast cancer.[32] Dendritic cells may transport bacteria to the breast tissue through intestinal translocation.[29] BC metastasis is associated with an increase in circulating lipopolysaccharide (LPS), which can activate monocytes and promote endothelial adhesion of

circulating cancer cells.[33] Infection of mice deficient in *Rag2*-deficient C57BL/6 *Apc*$^{min/+}$ with the enteric bacterial pathogen *Helicobacter hepaticus* significantly induces breast cancer and increases the frequency of intestinal adenoma through tumor necrosis factor α (TNFα)-dependent mechanisms.[29] Chronic inflammation, which is associated with tumor growth, is believed to be the mechanism by which gut bacteria can promote breast cancer.[32] Xuan et al. found that *Methylobacterium radiotolerans* was enriched in breast tumor tissue, while the total bacterial DNA load in the tumor was reduced compared to paired healthy breast tissue. Interestingly, the bacterial DNA load was inversely associated with advanced disease, which could have implications in breast cancer diagnosis and staging.[34] The gut microbiota can influence the clinical outcomes and side effects of primary breast cancer treatment.[37] Cachexia, a wasting syndrome, is associated with significant changes in the composition and diversity of the intestinal microbiota in mouse models of leukemia and colon cancer.[38] Animal studies suggest that the intestinal microbiota plays a role in the pathogenesis and manifestation of cancer cachexia, but human data is limited.[38] Studies have shown significant differences in the gut microbiota composition of colorectal cancer patients compared to healthy individuals, characterized by higher species richness and an increase in many potentially carcinogenic species (such as Fusobacterium, Bacteroides, Porphyromonas and Escherichia) and a decrease in potentially protective species.[39] *F. nucleatum*, for example, can adhere to and invade colonic epithelial cells and promote carcinogenesis through the action of FadA, which can bind to E-cadherin, activate β-catenin signaling, and modulate inflammatory and oncogenic responses.[36,40] *Enterococcus faecalis* has also been found to be significantly higher in patients with colorectal cancer compared to healthy individuals.[41] A study conducted by Khodavardi et al. in 2021 investigated the relative frequency of enterotoxigenic *B. fragilis* and *E. faecalis* in colorectal tissue samples from colorectal cancer patients and healthy individuals, revealing a significant increase in these bacteria in individuals with colorectal cancer. The frequency of these bacteria was higher in the advanced stages (III/IV) of cancer compared to the early stages (I/II).[42]

In a study conducted by Ellatif and colleagues in 2022, the probiotic efficacy and anticancer activities of *Lactiplantibacillus plantarum* ESSG1 (MZ683194.1) and *Lactiplantibacillus pentosus* ESSG2 (MZ683195.1), isolated from dairy products, were evaluated. Their study showed that strains 12B and 13B with 16S rRNA sequencing as *L. plantarum* ESSG1 (MZ683194.1) and *L. pentosus* ESSG2 (MZ683195.1) were the most promising, and their extracts were excellent, safe, and effective substitutes for antimicrobial, antioxidant, and anti-tumor agents.[43] In the study by Kumar Bhukya, the anticancer effects of the probiotic bacterium *Pediococcus pentosaceus* OBK05 were investigated. It was found that this specific bacterium has anticancer properties and by inhibiting the transfer from G1 to S phase, it can stop the cell cycle. In addition, the anticancer activities of this bacterium *in vivo* were confirmed in BALB/c mouse models.[44]

Alan and his colleagues, in 2022, concluded that the postbiotic metabolites of all strains of *Leuconostoc pseudomesenteroides* had good anticancer activity, with Y4 and Y6 generally showing better activity than control groups. Therefore, the Y6 strain, which had the best probiotic properties, exhibited good biological activity. It is believed that this isolate will be supported by new *in vivo* studies and ultimately be used in the food and health industries.[45]

Various metabolites derived from gut bacteria, such as butyrate and secondary bile acids, have different effects on colorectal carcinogenesis.[36] Recent studies have shown a significant relationship between colorectal cancer development and gut microbiota. The dietary risk of colorectal cancer is probably related to the dysbiosis of gut microbiota and their metabolites and can be a factor in the initiation and progression of colorectal cancer. Secreted bacterial toxins have been shown to increase the risk of cancer through toxin-mediated DNA damage.[46,47] The gut microbiota has also been implicated in pancreatic diseases, including acute pancreatitis, chronic pancreatitis, and pancreatic cancer, although human data is still limited.[48] Recent data suggest that the gut microbiota is involved in the metabolism of chemotherapy drugs and the tumor microenvironment, which can affect the efficacy of conventional chemotherapy and immunotherapy for pancreatic cancer. Chemotherapy can induce intestinal inflammation and changes in permeability, leading to alterations in the gut microbiome composition, including reduced diversity and a shift towards species associated with proinflammatory activity. The imbalanced gut microbiota can contribute to inflammation and psychological distress following chemotherapy.[31] Several bacterial metabolites have been found to potentially regulate pancreatic cancer, immune system function, and treatment resistance.[35] Microbacterium and Stenotrophomonas have been detected in pancreatic cancer tissues and are connected to microbes found in feces and saliva. *Klebsiella pneumoniae* was abundant in the stool microbiota of pancreatic ductal adenocarcinoma patients.[30] Overall, dysbiosis of the gut microbiota, particularly a reduction in SCFA-producing bacteria, worsens the severity of acute pancreatitis in both patients and mice.[28] Removing *E. coli* through ciprofloxacin treatment has been observed to enhance the anticancer effects of gemcitabine in a mouse cancer model.[30] Consequently, targeting the intestinal microbiota holds promise as a new treatment approach for cancer patients.[27] The microbiota may also serve as an effective, non-invasive, cost-effective, and suitable biomarker for cancer prognosis.[39] Table 1 lists some of the anticancer properties associated with probiotic species.

Table 1. The Anticancer Properties of Probiotic Species

Probiotic	Type of cancer	Effects	Ref.
VSL#3, Lactobacillus acidophilus, Bifidobacteria longum, L. gasseri	Colorectal cancer	Reduction of tumor burden and size	84
L. acidophilus, B. bifidum and B. infantum		Reducing tumor incidence, tumor multiplicity, tumor size and preventing colorectal cancer progression	85
L. salivarius Ren		Antimicrobial effects against carcinogenic microorganisms, anti-genotoxic activities against internal and external carcinogens, activation of intestinal mucosal immune system and anti-tumor effects.	75
L. rhamnosus GG, *Escherichia coli* Nissle 1917 and heat-inactivated VSL#3	Hepatocellular Carcinoma	Induction of anti-inflammatory cytokine IL-10 secretion and suppression of Th17 cell differentiation in intestine, modulation of intestinal microbiota and reduction of angiogenesis in liver tumor and tumor growth arrest	97
L. plantarum		Reducing the expression of TLR4, CXCL9 and PREX-2, reducing the expression of TLR-induced inflammation and improving liver function	91,98
L. plantarum	Gastric cancer	Reducing the expression of AKT gene and increasing the expression of PTEN gene, inhibition of gastric cancer related to Helicobacter pylori	101
L. plantarum and L. rhamnosus		Increasing the expression of MUC2 and MUC3 genes, restoring the permeability of the gastric mucosa and inhibiting the adhesion of pathogenic bacteria, including H. pylori.	101
L. reuteri		Reducing the expression of uPA and uPAR genes involved in cancer metastasis, inhibiting the proliferation of cancer cells	106
L. strains		Reducing the attachment and invasion of H. pylori to gastric epithelial cells and reducing the production of interleukin 8	107
Lactobacilli	Esophageal cancer	Modulatory effects on signaling pathways related to cancer, apoptosis, metastasis and cell cycle control	109,161
L. rhamnosus		Inhibition of tumor growth by affecting genes involved in signal transduction pathways	118
L. s acidophilus	Breast Cancer	Stimulating immune responses by producing proinflammatory cytokines such as IFN-γ and inhibiting the production of anti-inflammatory cytokines such as IL-4 and IL-10 anticancer activity in mammary tumor bearing mice	162,163
B. animalis, L. acidophilus, B. infantis, L. paracasei, B.bifidum		Reduction of cancer cell growth in MCF 7 cells	14,164
Streptococcus thermophilus		Reducing DNA damage and neutralizing reactive oxygen species, anticancer properties	165,166
L. helveticus R389		Immune system response modulator in BC carrier mice	167
L. plantarum		Increasing the level of IFN-γ and IL-2 and increasing the activity of NK cells, inhibiting tumor progression	168,169
Butyricicoccus pullicaecorum	Bladder Urothelial cancer	Regulation of cell cycle and apoptosis and molecular effects of butyrate on urinary bladder cancer, induction of anticancer effect and prevention of cancer progression	141
L. casei and L. rhamnosus GG	Bladder Urothelial cancer	Cytotoxic effect on growth, prevention of bladder cancer	140,144
Lactobacillus and pediococcus	Cervical cancer	Production anticancer metabolites such as short-chain fatty acids, lactic acid and bacteriocin anticancer activity	170

Immunomodulatory Activity of Probiotics

One particularly appealing aspect of probiotics is their ability to modulate the immune system. Consequently, several probiotic species have been utilized in the production of functional dairy products, aiming to maintain immune homeostasis in the host.[49] *Lactobacillus* and *Bifidobacterium* are the predominant probiotic microorganisms used in the food and pharmaceutical industries, with various strains from these genera demonstrating beneficial properties.[50] Studies have shown that probiotics can increase the proliferation of spleen cells in mice, specifically T and B cells, in response to mitogens. They also stimulate the production of cytokines such as TNF-α, IL-1β, IL-12, IL-6, and IFN-γ in immune cells.[51,52] Furthermore, probiotics have been found to activate natural killer (NK) cells by promoting IL-12 production by monocytes/macrophages.[53] The immunomodulatory properties of probiotics have been demonstrated in inducing the production of IL-10 and regulatory T (Treg) cells, thereby reducing allergies, inflammatory bowel disease (IBD), autoimmune diseases, and inflammatory responses.[54] In addition, certain non-pathogenic strains of *E. coli* (G3/10), known as probiotics, have been shown to inhibit the growth of pathogenic bacteria and secrete potent antimicrobial peptides like bacteriocin and microcin S. These antimicrobial substances are effective against harmful gastrointestinal pathogens such as *Helicobacter pylori*, Campylobacter, *Clostridium difficile*, and rotavirus.[55] Probiotics can also enhance the immune system's response to colon cancer by inducing the production of interferon-gamma (IFN-γ) and interleukin-10 (IL-10) in a mouse model of 1,2-dimethyl hydrazine (DMH)-induced colon cancer.[56] Notably, probiotics have been observed to decrease the production of interferon-γ (INF-γ) and TNF-α by Peyer's patch lymphocytes, while reducing the production of proinflammatory cytokines by spleen cells in mice. Treatment with a combination of *L. paracasei* and *L. reuteri* in IL-10-deficient mice infected with *H. hepaticus* resulted in reduced mucosal proinflammatory cytokines and a subsequent decrease in colitis development.[57]

Furthermore, the increased secretion of IL-2 by *L. plantarum* KLDS1.0318 has been found to stimulate T cell proliferation and IFN-γ production, thereby enhancing the immune response against cancer and pathogen-infected cells.[51] Polysaccharide A, present on the surface of vesicles secreted by *B. fragilis*, directly signals through TLR2 on Foxp3+ regulatory T cells, promoting immune tolerance and the conversion of CD4(+) T cells into Foxp3(+) cells. This induction of Treg cells leads to an IL-10 response in intestinal T cells, inhibiting the expansion of TH17 cells responsible for intestinal wall disruption and reducing intestinal inflammation.[58-60] Additionally, *Bifidobacterium infantis* has been found to effectively reduce chemotherapy-induced intestinal mucositis by suppressing Th1 and Th17 responses and promoting the response of CD4+ CD25+ Foxp3+ regulatory T cells.[61] *In vitro* analyses using immune cells have demonstrated that the exopolysaccharide (EPS) synthesized by *F. prausnitzii* HTF-F mediates its anti-inflammatory potential through the production of IL-12 and IL-10 in antigen-presenting cells, in a TLR-2-dependent manner. Similarly, the EPS synthesized by *Bifidobacterium adolescentis* IF1-03 can modulate the Treg/Th17 axis regulated by macrophages, providing protection against DSS-colitis in mice.[57] There is increasing evidence suggesting that probiotics, through their interaction with Toll-like receptors (TLRs), stimulate the production of proinflammatory cytokines, induce TNF production in epithelial cells, inhibit NF-κB activation in macrophages, and affect the requirements for neutrophil use.[62] Probiotics can also inhibit the binding of lipopolysaccharides to the CD14 receptor, thus reducing overall NF-κB activation and the production of proinflammatory cytokines.[63] Recently, seven peptides from the supernatant of *F. prausnitzii*, collectively known as microbial anti-inflammatory molecule (MAM), have been identified. These peptides have demonstrated the ability to inhibit the NF-κB pathway *in vitro* and exhibit anti-inflammatory properties in a DiNitroBenzene Sulfate (DNBS)-induced colitis model.[58] Probiotics have been extensively studied and have been reported to modulate humoral, cellular, and non-specific immunity, while also enhancing the immune barrier.[54] The bacterial cells of probiotics and their soluble factors likely induce systemic immune responses by stimulating antigen-presenting cells in the gastrointestinal tract.[53] Lactobacillus species, such as *L. plantarum* and *L. salivarius* CICC 23174, have been found to significantly increase the proliferation of spleen cells, enhance the conversion rate of spleen lymphocytes, promote the production of secretory IgA (sIgA), and increase the number of CD11c+ CD80+ positive cells, thereby influencing immune activities.[51-64] It has been reported that the administration of probiotics leads to a significant increase in IgA and IgG concentrations in mice, although this effect is dose-dependent.[54] Furthermore, the oral administration of *Bacillus polyfermenticus* to humans stimulates IgG production and modulates the number of CD4+, CD8+, or natural killer (NK) cells.[65] Probiotics have the ability to modulate dendritic cells (DCs) into regulatory cells, contributing to immune tolerance and balance. DCs can uptake probiotics and present short antigenic peptides to T cells, thereby stimulating the differentiation of Th1, Th2, Th17, and/or Treg cells.[55] Exposure of dendritic cells to *Bifidobacterium bifidum* cell wall extracts has been observed to induce Treg differentiation.[57] *Bifidobacterium breve* has been shown to promote the generation of IL-10-producing T cells, with this effect being mediated by CD103+ DCs.[66] Probiotic lactobacilli have the ability to stimulate macrophages and dendritic cells, leading to the secretion of cytokines such as IL-12 and IL-10, which help regulate the host's immune responses.[49] Lactic acid bacteria can also promote the production of IFN-γ by NK cells through the involvement of dendritic cells.[60] Binding of lipopolysaccharides (LPS) to toll-like receptors (TLR 2 and 4) on endothelial cells, dendritic cells, and macrophages results in activation and increased expression of inflammatory markers. Treatment with probiotics can help reduce intestinal dysbiosis and intestinal permeability, thereby reducing the production of inflammatory biomarkers and mitigating immune system overstimulation The prominent mechanisms through which probiotics exert their immune and biological effects involve the increase of anti-inflammatory cytokines and T-regulatory (Treg) cells, along with the reduction of proinflammatory cytokines.[67]

Lactobacillus and *Bifidobacterium* species play a crucial role in innate immunity by enhancing the cytotoxicity of natural killer cells, promoting macrophage phagocytosis, interacting with enterocytes and dendritic cells, and modulating acquired immunity through interactions with Th1, Th2, and Treg cells.[54] *F. prausnitzii* inhibits IL-1β-induced IL-8 secretion in Caco-2 cells and induces IL-10, which inhibits the production of proinflammatory cytokines. Bacteroidetes has also been shown to suppress proinflammatory IL-17.[68] Moreover, *L. plantarum* CGMCC 1.557 has been found to be the most active strain in enhancing macrophage phagocytic activity, while *L. salivarius* CICC 23174 is the most effective strain in maintaining Th1/Th2 balance.[64] Clinical and preclinical observations have demonstrated the anti-inflammatory activity of *L. plantarum* and its potential in regulating host immune responses upon ingestion.[69] Recently, two new probiotic Lactobacillus strains (s193 and s292) have been found to increase β-8 integrin on mesenchymal dendritic cells, thereby strongly promoting the differentiation of CD4+ T cells into Treg cells.[55]

Lactococcus lactis expressing pili proteins from *B. bifidum* has been associated with decreased IL-10 and increased tumor necrosis factor α (TNFα) in an *in vivo* mouse model, while the simultaneous use of flagellin and *L. casei* Shirota strain increased IL-12 production.[57] Two proteins (p75 and p40) purified from the probiotic *L. rhamnosus* GG have been

shown to prevent TNF-induced epithelial cell apoptosis by activating Akt and inhibiting the activation of p38 mitogen-activated protein kinase (MAPK), thus promoting cell growth.[70] Furthermore, *B. adolescentis* SPM0212 has been found to enhance TNF production and may have utility in enhancing the immune system in the human intestinal tract.[71] *L. reuteri* ATCC PTA 6475 can suppress the production of TNF-α induced by LPS through the inhibition of the c-Jun pathway regulated by MAPK and activator protein-1.[60] *In vitro* studies using *L. salivarius* CICC 23174 and *L. plantarum* CGMCC 1.557 have demonstrated the effective inhibition of TNF-α-induced IL-8 production in Caco-2 cells, as well as the prevention of proinflammatory responses caused by *S. typhimurium*.[64] In a study using Caco-2 cells, it was observed that *L. sakei* induced the production of proinflammatory cytokines such as IL-1β, IL-8, and TNF-α, while *L. johnsonii* influenced the production of the anti-inflammatory cytokine TGF-β.[54] Another study by Lores et al. demonstrated that *L. lactis* NCDO 2118 reduced IL-1β-induced IL-8 secretion in Caco-2 cells, suggesting an anti-inflammatory effect. However, in mice with induced colitis, oral administration of *L. lactis* NCDO 2118 increased IL-6 levels in the colon. Interestingly, it ameliorated aberrant TNF-α levels induced by DSS (dextran sulfate sodium) almost to control levels, indicating an immunomodulatory effect.[66] Lactobacilli have been shown to enhance immunity in mice, but the effectiveness of a specific probiotic in modulating immunity can vary depending on the dose and strain. Furthermore, individual responses to probiotics may differ among people.[49,51] Animal and human studies have provided evidence that probiotics can significantly impact immune and inflammatory mechanisms. However, the precise underlying mechanisms are not yet fully understood.[60]

Effect of Probiotic Bacteria Strains on Anticancer Immune Response Based on *In Vivo* and *In Vitro* Studies

Colorectal Cancer

Colorectal cancer is a serious disease and one of the most common gastrointestinal malignancies. Its development has been associated with various environmental and genetic factors, including sedentary lifestyle, obesity, high body mass index (BMI), high-fat and low-fiber diets, alcohol consumption, smoking, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and family history. While surgery is the primary treatment for colorectal cancer, probiotics have emerged as a potential adjunct therapy for this condition.[20,72-74] These studies suggest a special relationship between probiotics and colorectal cancer, as probiotics can modulate the intestinal microbiota and prevent cancer development.[75] Probiotics exert their anticancer effects through various mechanisms, such as modifying the metabolic activities and physicochemical conditions of the large intestine, eliminating carcinogenic substances, producing anti-tumor or anti-mutagenic compounds, and enhancing the host's immune response.[76-78] The gut microbiome has a significant impact on the immune system, and several studies have highlighted the role of *F.nucleatum* in colorectal cancer. *F. nucleatum* can suppress the response of human T cells to mitogens and antigens, inhibit the cell cycle in the G1 phase, induce apoptotic cell death in certain immune cells, and modulate the tumor immune environment, thereby inhibiting tumor progression. The immunosuppressive effects of *F. nucleatum* may influence the mortality of colorectal cancer patients.[79-83] In a study by Compare and Nardone, probiotics including VSL#3, *L. acidophilus*, *Bifidobacterium longum*, and *L. gasseri* were found to improve colon cancer by reducing tumor burden and size. Consumption of inulin along with *B. longum* and *Bifidobacterium lactis* demonstrated a reduction in chemically-induced colorectal cancer and increased apoptotic response.[84] In another study by Kuugbee et al., the probiotics *L. acidophilus*, *B. bifidum*, and *B. infantum*, in combination with oligofructose and maltodextrin (referred to as LBB), modulated the intestinal microbiota and inhibited the expression of Cox-2 and β-catenin in an animal model of colorectal cancer. The results indicated that LBB prevented colorectal cancer progression by reducing tumor incidence, multiplicity, and size.[85] The use of a probiotic mixture is more effective than prescribing a single strain of a single probiotic, this is because probiotics increase the diversity of the intestinal microbiota and cause synergy between probiotic strains for better results and the promotion of a healthy natural microbiota by multi-strain probiotics.[86] In 2020, Kenfack Momo and colleagues investigated a new derivative of pyran with antioxidant and anticancer properties isolated from the probiotic strain *L. plantarum* H24. The compounds were screened for their antioxidant and cytotoxic activities against colon cancer cells (Caco-2), and they concluded that it could be a useful anticancer compound. Thus, *L. plantarum* H24 could be used for preventing oxidative stress and its related damages and improving human health.[87] In 2022, Sheng and colleagues investigated a new exopolysaccharide derived from the probiotic strain *L. pantheris* TCP102 with immune-boosting and anticancer activities. They demonstrated that these exopolysaccharides significantly induced the production of nitric oxide (NO), TNF-α, and IL-6 in Ana-1 cells and peritoneal macrophages, indicating immune-boosting and anticancer activities. Meanwhile, the exopolysaccharides significantly suppressed the proliferation of HCT-116, BCG-803, and especially A-2780 cells. The results suggest that the three new exopolysaccharides isolated from *L. pantheris* TCP102 can be considered as potential applications in functional foods and natural anti-tumor drugs.[88]

L. salivarius Ren has also shown promising effects in preventing colorectal cancer by exerting antimicrobial effects against cancer-causing microorganisms, exhibiting

anti-genotoxic activities against internal and external carcinogens, and activating the intestinal mucosal immune system. Zhang et al. demonstrated that *L. salivarius Ren* effectively countered adverse changes in the colon microbiota induced by dimethylhydrazine (DMH) injection and suppressed DMH-induced colon cancer in mice.[75]

Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and is often a severe complication of chronic liver disease. Recent studies, both experimental and clinical, have highlighted the significance of the gut-liver axis in the development of chronic liver diseases, including HCC. HCC typically arises in chronically damaged liver tissues as a result of ongoing inflammatory and regenerative processes that contribute to the initiation and progression of the disease.[89] Probiotics have emerged as a potential biological treatment for HCC. Probiotics consist of beneficial microorganisms that colonize the human intestines and reproductive system. By modulating the host's intestinal microbiota, probiotics promote the growth of beneficial microbes while inhibiting the growth of harmful microbes. This modulation of the gut microbiota has the potential to reduce the risk of HCC and can be used as a biological treatment approach.[90-94] Probiotics exert anticancer effects through various mechanisms, including the production of anticancer compounds, enhancement of the immune system, improvement of the intestinal barrier function, inhibition of cancer cell proliferation, and induction of apoptosis in cancer cells. Consumption of probiotic strains that promote health can help improve liver disorders that may arise from interactions between bacterial components and liver receptors.[94-96] In a study by Li et al., a novel probiotic mixture called Prohep, which includes *L. rhamnosus* GG, *E. coli* Nissle 1917, and heat-inactivated VSL#3, significantly reduced HCC growth in mice. Prohep exerted its anti-tumor function by inducing the secretion of the anti-inflammatory cytokine IL-10, suppressing Th17 cell differentiation in the intestine, modulating the intestinal microbiota, depleting Th17 cells from the intestine, and attenuating angiogenesis in liver tumors, ultimately leading to suppressed tumor growth.[97] In an *in vitro* study by Elshaer, early administration of *L. plantarum* in Wistar rats with thioacetamide-induced liver cirrhosis resulted in reduced expression of Toll-like receptor 4 (TLR4), CXCL9, and PREX-2, along with improved liver function. The decreased expression of TLR4 indicated reduced inflammation.[91,98] Another study by Kumar et al. investigated the chemopreventive effect of milk fermented with probiotics and chlorophyllin on HCC induced by aflatoxin B1 (AFB1) in rats. The use of probiotics led to decreased levels of c-myc, bcl-2, cyclin D1, and ras-p21, as well as reduced incidence of HCC. This study demonstrated the protective capacity of probiotics against AFB1-induced liver cancer.[99] In addition to directly modulating the intestinal microbiota, probiotics can exert their anticancer effects by modulating immunity, reducing bacterial translocation, improving intestinal barrier function, and exhibiting anti-inflammatory and anti-pathogenic activities. They also contribute to the reduction of tumor formation and metastasis.[92,100]

Gastric Cancer

Gastric cancer is a leading cause of death globally, and *H. pylori* infection is often involved in its development as it colonizes the stomach mucosa.[101] Probiotics have shown potential in improving *H. pylori*-related diseases. They can modulate immune responses, including neutrophils, lymphocytes, plasma cells, and macrophages, and stimulate inflammatory responses against *H. pylori*. Probiotics can significantly increase the levels of proinflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, and tumor necrosis factor α in the gastric mucosa.[101-103] Probiotics can prevent the proliferation of *H. pylori* by competing with the bacteria for host surface receptors, thus impairing its adhesion to epithelial cells. Additionally, probiotics can combat *H. pylori* through the secretion of antibacterial compounds, including lactic acid, bacteriocins, hydrogen peroxide, short-chain fatty acids, and antibiotic-like substances such as rotrin and rotricycline.[101,103] Lactobacillus and Bifidobacterium are among the most commonly used probiotic bacteria, and lactobacilli, in particular, have been shown to inhibit *H. pylori* through various immunological and non-immunological mechanisms.[101,104,105] Studies have investigated the effects of probiotics on stomach cancer. Maleki-Kaklar et al. demonstrated that probiotics, especially *L. plantarum*, may play a role in *H. pylori*-associated gastric carcinogenesis by regulating the PTEN/AKT signaling pathways [101]. Laboratory studies with probiotics such as *L. plantarum* and *L. rhamnosus* have shown increased expression of MUC2 and MUC3 genes, indicating their ability to restore gastric mucosal permeability and inhibit the adhesion of pathogenic bacteria.[101] Rasouli and colleagues showed that *L. reuteri* can reduce the expression of uPA and uPAR genes involved in cancer metastasis, thereby inhibiting cancer cell proliferation.[104] The results of the studies by Rasouli et al., showed that *L. reuteri* is able to reduce the expression of uPA and uPAR genes, which are involved in cancer metastasis, and can show beneficial effects by inhibiting the proliferation of cancer cells.[106] Chen et al. found that treatment with Lactobacillus strains significantly reduced the attachment and invasion of *H. pylori* to gastric epithelial cells, as well as the production of IL-8.[107] Zhang et al. demonstrated that *L. gasseri* inhibits the secretion of proinflammatory cytokines TNF and IL-6 in macrophages, and probiotics play a role in inhibiting pathogens by increasing IgA levels and strengthening the mucosal barrier.[108]

Esophageal Cancer

Esophageal cancer is a serious malignancy affecting the tissue of the esophagus, and it is classified into two main types: squamous cell carcinoma and adenocarcinoma.[109] Squamous cell carcinoma typically occurs in the upper or middle part of the esophagus, while adenocarcinoma arises from gland cells in the lower esophagus.[110] As the cancer progresses, patients may experience symptoms such as chronic cough, indigestion, vomiting, fatigue, and heartburn.[109-113]

Research has indicated that the microbial diversity in the esophagus undergoes significant changes during esophagitis or esophageal cancer. The abundance of streptococcal species decreases, while gram-negative anaerobic bacteria or microaerophiles such as Peperamella, Prevotella, Fusobacterium, and Neisseria increase in esophageal cancer.[114] Deng et al. observed a decrease in energy metabolism pathways in patients with esophageal cancer compared to healthy individuals. Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are common metabolites produced by bacteria in the gastrointestinal tract. SCFAs are considered important regulators of inflammation, differentiation, and apoptosis in host cells, and they play a crucial role in bacterial energy metabolism and overall health. Furthermore, SCFAs act as molecular signals and exhibit anticancer properties.[115-117] Deng's study also showed that patients with esophageal cancer had high abundances of Firmicutes and Actinobacteria, but decreased levels of Bacteroides, leading to an increased ratio of Firmicutes to Bacteroides. These changes in the intestinal microbiota may be associated with dysbiosis and inflammation in patients with esophageal cancer.[115]

Lactobacilli are commonly used probiotic microorganisms known for their potent anti-tumor properties. They can kill many cancer cells through cytoplasmic extracts, heat-killed cells, and cell wall peptidoglycans. Cytoplasmic extracts of *L. casei* and Bifidobacterium have been shown to affect the growth of cancer cell lines and inhibit cancer cell proliferation. *L. rhamnosus* has also been found to inhibit tumor growth by affecting genes involved in signal transduction pathways.[109,118,119] Signal transduction pathways play a crucial role in the initiation and progression of cancer, and targeting these pathways can be a promising approach for cancer treatment. The Wnt pathway, in particular, is a critical signaling pathway that is often dysregulated by mutations in various cancers.[120-123]

Breast Cancer (BC)

Breast cancer (BC) is one of the most common cancers in women, and various factors such as genetics, hormone replacement therapy, lifestyle, eating habits, and age contribute to its development.[124,125] Several animal studies have demonstrated the beneficial effects of probiotics against BC. For instance, oral administration of *L. acidophilus* can stimulate immune responses by producing proinflammatory cytokines like IFN-γ and inhibiting the production of anti-inflammatory cytokines such as IL-4 and IL-10. Other animal studies have reported that oral administration of *L. acidophilus* exhibits anticancer activity in mice with mammary tumors.[126,127] The microbiota plays a crucial role in maintaining overall health, and disruption of the microbiota can lead to pathobiological changes, including BC. Gastrointestinal bacteria have an important role in modulating estrogen levels by influencing the reabsorption of estrogens, the liver-intestinal blood circulation, and the production of β-glucuronidase, an enzyme involved in the conversion of estrogen into its free form.[128-130] Probiotics can serve as natural agents for cancer treatment, and specific strains such as *Bifidobacterium animalis*, *L. acidophilus*, *B. infantis*, *L. paracasei*, and *B. bifidum* have been shown to inhibit the growth of cancer cells in MCF7 cells.[131,132] Lactobacillus and Streptococcus are more commonly found in the breast microbiota of healthy individuals, and these bacteria play a role in regulating tumor progression by stimulating the activity of natural killer (NK) cells. Additionally, *Streptococcus thermophilus* produces antioxidants that exhibit anticancer properties by reducing DNA damage and neutralizing reactive oxygen species (ROS).[133,134]

In a study by Alejandra et al., an *in vitro* study involving BC-bearing mice demonstrated that oral administration of fermented milk containing *L. helveticus* R389 elicited an immunomodulatory response, suggesting its potential use as immunoadjuvant therapy for protection against malignancies.[135] In 2022, Pakbin and colleagues investigated the anticancer properties of the supernatant of *Saccharomyces boulardii* probiotic on human breast cancer cells. They found that suppression of survivin gene expression should be one of the main molecular tumor suppression mechanisms that help induce apoptosis in breast cancer cells. However, the anticancer activity of supernatant of *S. boulardii* was more effective against MCF-7 cells than MCF-7/MX cells. They suggested that the supernatant of *S.* be considered as a future anticancer drug for the treatment of human breast cancer. Further research, especially *in vivo* studies, are strongly recommended to identify other tumor-suppressing mechanisms of SBS against breast carcinoma.[136] In 2021, Vinothkanna studied the properties, antioxidant and anticancer activities of exopolysaccharides produced by the probiotic *Bacillus albus* DM-15, isolated from Ayurvedic Fermented Dasamoolarishta. They found that the exopolysaccharide produced by the probiotic *B. albus* DM-15 exhibited promising cytotoxic activity against lung cancer cells (A549), and subsequent cellular staining showed the characteristics of necrosis and apoptosis in damaged A549 cells. The purified exopolysaccharide from *B. albus* DM-15 could be further studied and used as a potential carbohydrate polymer in food, cosmetic, pharmaceutical, and biomedical applications.[137]

Another study by Yazdi et al. investigated the administration of selenium nanoparticles enriched with *L. plantarum* in mice, showing increased levels of IFN-γ and IL-2, as well as enhanced activity of NK cells, which were beneficial in inhibiting tumor progression. Furthermore, Yazdi et al. conducted another study demonstrating that oral administration of selenium nanoparticles enriched with *L. brevis* resulted in improved prognosis among mice with highly metastatic breast tumors.[138,139]

Bladder Cancer

Bladder cancer is a common malignancy associated with significant morbidity and mortality, with major risk factors including environmental or occupational exposure to carcinogens, particularly tobacco. Bladder cancer can be categorized into different histological types, including urothelial carcinoma, adenocarcinoma, small cell carcinoma, plasmacytoid carcinoma, and squamous cell carcinoma. The disease is also divided into two main categories: non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). The microbiome has diverse effects on bladder cancer at different stages of its development and modulates the endogenous antitumor immune response, making it a potential biomarker and therapeutic target in bladder cancer.[140] The microbiota isolated from the urine of bladder cancer patients is associated with bladder tumors, and certain bacteria found in urine may serve as therapeutic targets for bladder cancer. Most of the microbiota resides in the colon, where they play a clinically important role in human health and pathogenesis. Dysbiosis in the colon has been implicated in the regulation of bladder cancer.[141-143] Butyrate, a short-chain fatty acid (SCFA), is a potent inhibitor of bladder cancer proliferation. It is synthesized from dietary carbohydrates through bacterial fermentation in the colon. Butyrate may impact the expression of tumor suppressors involved in chemotherapy treatment.[141,142] In a study by Wang et al., *Butyricicoccus pullicaecorum* was found to induce its anticancer effect and inhibit cancer progression by regulating cell cycle and apoptosis. Supplementation with *B. pullicaecorum*, which secretes the specific SCFA butyrate, may offer therapeutic opportunities for various bladder cancers.[141] Recent studies have explored the effects of probiotics on bladder cancer. For example, Seow et al. discovered that Lactobacillus species, especially *L. casei* and *L. rhamnosus* GG (LGG), exert a cytotoxic effect that inhibits the growth of bladder cancer cells.[140,144] Kandasamy et al. suggested that lactobacilli can stimulate the immune system through actions such as stimulating neutrophils to secrete cytokines, promoting dendritic cell maturation, and inducing the production of antigen-specific cytotoxic T cells against cancer cells. Using selected bacteria to induce antigen-specific cytotoxicity could potentially become another therapeutic option against cancer cells, alongside recombinant cytokines.[140,145] In an *in vitro* study by Fraglie et al., recombinant Salmonella was utilized to treat bladder cancer in mice. They inserted IL-2 or/and TRAIL genes into the genome of an attenuated Salmonella strain (SL3261) and investigated the effect of this recombinant strain on bladder cancer in mice. The study found that the recombinant strain SL3261 caused cell membrane damage, increased nitric oxide (NO) production, and promoted apoptosis in mouse bladder cancer M49 cells.[146,147]

Cervical Cancer

Cervical cancer is a common malignancy that poses a significant threat to women's health. It is one of the leading malignant tumors of the female genital tract and is often diagnosed between the ages of 35 and 44, in middle age. In the early stages, cervical cancer is typically asymptomatic, but as it progresses, symptoms such as discomfort during intercourse, pelvic pain, irregular vaginal bleeding, fatigue, and leg swelling may arise.[148,149] Studies have demonstrated that alterations in the vaginal microbiome play a crucial role in the development of cervical cancer. Additionally, the presence of probiotics can affect the clearance of human papillomavirus (HPV), a potential cause of cervical cancer, and induce apoptosis of cancer cells and other anticancer activities. Thus, probiotics play an important role in fighting against cancer.[150-152] The immune system plays a critical role in preventing and controlling cancer cells. Bacteria can influence the immune system in various ways, including inducing the production of gamma interferon by T helper cells, increasing immunoglobulin A (IgA) secretion, boosting the number of natural killer (NK) cells, and enhancing phagocytic activity. A balanced relationship between the host's immune system and the microbiota present in the genital tract is necessary, as any disruption in this balance can lead to cervical cancer, particularly in the presence of infectious agents.[152,153] Lactobacillus and Pediococcus are lactic acid bacteria known as probiotics Lactobacillus is the most abundant natural flora associated with the vaginal mucous surface. By binding to the vaginal epithelium, it competes against the colonization of pathogens. Additionally, Lactobacillus produces lactic acid, which helps maintain the acidic pH of the vagina, stabilizes the vaginal bacterial flora, and prevents diseases. Therefore, it has been introduced as a vaginal probiotic.[149,154,155] Numerous studies have demonstrated that probiotic bacteria such as *L. casei*, *L. plantarum*, *L. rhamnosus* GG, and *L. acidophilus* exert their anticancer effects by activating NK cells and promoting dendritic cell maturation. For instance, a study by Dallal et al. showed that milk containing *L. rhamnosus* and *B. lactis* can increase NK cell activity in elderly individuals.[156] Oral administration of *L. casei* has been found to significantly increase the production of IL-12, interferon-gamma, and NK cells in mice with cancer.[152]

Bacteria can inhibit the cell cycle through various mechanisms and prevent the proliferation of cervical cancer cells. For example, *Bacillus anthracis* and *Bordetella pertussis* secrete adenylate cyclase toxins, which reduce the expression of Cyclin D1, a factor that inhibits the cell cycle. The cycle inhibitory factor (Cif) produced by *E. coli* also causes cell cycle arrest. Studies have shown that *L. casei* can regulate G1/S checkpoints by reducing the expression of Cyclin E1, while Bifidobacterium breve reduces the expression of Cyclin D1 and E1.[157] Moreover, there are mechanisms that prevent the migration of tumor cells. For example, Li et al. reported that incubation of Hela and U14 cell lines with lactobacilli can inhibit cell migration. This inhibitory effect was attributed to increased expression of E-cadherin protein and inhibition of tumor cell invasion.[158] Nowak and colleagues in 2022 conducted a laboratory study titled "Anticancer potential of post-fermentation media and cell extracts of probiotic strains." Their aim was to evaluate the anti-proliferative mechanism of post-biotics, post-fermentation media (PFM), and cell extracts (CEs) of multiple strains of lactic acid bacteria on colon (Caco-2) and cervical (HeLa) cancer cell lines. They found that these strains had anticancer activity, and the anticancer activity of PFM and CEs LAB and the ability to induce apoptosis were specific to certain strains.[159]

In another study, it was found that *Pseudomonas aeruginosa* mannose-sensitive hemagglutinin (PA-MSHA) can arrest HeLa cells in the G2/M phase, ultimately preventing cell invasion and metastasis.[160]

Conclusion

The modulation of the immune system is regarded as a crucial health benefit associated with probiotics. Several probiotic strains, such as *B. animalis*, *L. acidophilus*, *B. infantis*, *L. paracasei*, *B. bifidum*, *L. plantarum*, *L. paracasei*, *and B. longum*, have been found to possess the ability to inhibit the growth of cancer cells. Consequently, these probiotics have potential applications as natural agents for cancer treatment, leading to a reduction in tumor incidence, tumor multiplicity, and tumor size. Additionally, probiotics have been shown to downregulate the expression of genes involved in cancer metastasis. By inhibiting the proliferation of cancer cells, probiotics exhibit beneficial effects in combating cancer.

Authors' Contributions

RG, MK, and HEGG contributed to design of study. RG, MK, MAA, HEGG, and HMH performed acquisition and evaluation of data, and preparation of the manuscript. All authors read and approved the final manuscript.

Ethical Approval

This study was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences (IR.BMSU.BLC.1401.054).

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

References

1. Daillère R, Derosa L, Bonvalet M, Segata N, Routy B, Gariboldi M, et al. Trial watch: the gut microbiota as a tool to boost the clinical efficacy of anticancer immunotherapy. Oncoimmunology. 2020;9(1):1774298. doi:10.1080/2162402X.2020.1774298
2. Rowland IR. The role of the gastrointestinal microbiota in colorectal cancer. Curr Pharm Des. 2009;15(13):1524-7. doi:10.2174/138161209788168191
3. Raskov H, Burcharth J, Pommergaard HC. Linking gut microbiota to colorectal cancer. J Cancer. 2017;8(17):3378-95. doi:10.7150/jca.20497
4. Plaza-Diaz J, Gomez-Llorente C, Fontana L, Gil A. Modulation of immunity and inflammatory gene expression in the gut, in inflammatory diseases of the gut and in the liver by probiotics. World J Gastroenterol. 2014;20(42):15632-49. doi:10.3748/wjg.v20.i42.15632
5. Maukonen J, Saarela M. Human gut microbiota: does diet matter?. Proc Nutr Soc. 2015;74(1):23-36. doi:10.1017/S0029665114000688
6. Yoo JY, Groer M, Dutra SV, Sarkar A, McSkimming DI. Gut microbiota and immune system interactions. Microorganisms. 2020;8(10):1587. doi:10.3390/microorganisms8101587
7. Akbar N, Khan NA, Muhammad JS, Siddiqui R. The role of gut microbiome in cancer genesis and cancer prevention. Health Sci Rev. 2022;2:100010. doi:10.1016/j.hsr.2021.100010
8. Bultman SJ. Emerging roles of the microbiome in cancer. Carcinogenesis. 2014;35(2):249-55. doi:10.1093/carcin/bgt392
9. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. Gut. 2019;68(8):1417-29. doi:10.1136/gutjnl-2018-317609
10. Chen D, Jin D, Huang S, Wu J, Xu M, Liu T, et al. *Clostridium butyricum*, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. Cancer Lett. 2020;469:456-67. doi:10.1016/j.canlet.2019.11.019
11. Meng C, Bai C, Brown TD, Hood LE, Tian Q. Human gut microbiota and gastrointestinal cancer. Genom Proteom Bioinform. 2018;16(1):33-49. doi:10.1016/j.gpb.2017.06.002
12. Cammarota G, Ianiro G. Gut microbiota and cancer patients: a broad-ranging relationship. Mayo Clinic Proceedings: Elsevier 2017. pp. 1605-7. doi:10.1016/j.mayocp.2017.09.009
13. Namiki M. Antioxidants/antimutagens in food. Crit Rev Food Sci Nutr. 1990;29(4):273-300. doi:10.1080/10408399009527528
14. Hirayama K, Rafter J. The role of probiotic bacteria in cancer prevention. Microbes Infect. 2000;2(6):681-6. doi:10.1016/S1286-4579(00)00357-9
15. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. doi:10.3322/caac.20107
16. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell. 1996;87(2):159-70. doi:10.1016/

S0092-8674(00)81333-1
17. Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978–2012. Int J Cancer. 2020; 147(2):317-30. doi:10.1002/ijc.32723
18. Hsu WH, Chang CC, Huang KW, Chen YC, Hsu SL, Wu LC, et al. Evaluation of the medicinal herb *Graptopetalum paraguayense* as a treatment for liver cancer. PLoS One. 2015;10(4):e0121298. doi:10.1371/journal.pone.0121298
19. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piceros M, et al. Global cancer Observatory: cancer today. Lyon, France: international agency for research on cancer. 2018;3(20):2019.
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6): 394-424. doi:10.3322/caac.21492
21. Behrouzi A, Ashrafian F, Mazaheri H, Lari A, Nouri M, Rad FR, et al. The importance of interaction between MicroRNAs and gut microbiota in several pathways. Microb Pathog. 2020;144:104200. doi:10.1016/j.micpath.2020.104200
22. Tsai YT, Cheng PC, Fan CK, Pan TM. Time-dependent persistence of enhanced immune response by a potential probiotic strain *Lactobacillus paracasei* subsp. paracasei NTU 101. Int J Food Microbiol. 2008;128(2):219-25. doi:10.1016/j.ijfoodmicro.2008.08.009
23. Jacouton E, Chain F, Sokol H, Langella P, Bermudez-Humaran LG. Probiotic strain *Lactobacillus casei* BL23 prevents colitis-associated colorectal cancer. Front Immunol. 2017;8:1553. doi:10.3389/fimmu.2017.01553
24. Mattar MC, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel disease and colorectal cancer. Gastrointest Cancer Res. 2011;4(2):53-61.
25. Plaza-Díaz J, Álvarez-Mercado AI, Ruiz-Marín CM, Reina-Pérez I, Pérez-Alonso AJ, Sánchez-Andujar MB, et al. Association of breast and gut microbiota dysbiosis and the risk of breast cancer: a case-control clinical study. BMC Cancer. 2019;19:495. doi:10.1186/s12885-019-5660-y
26. Vivarelli S, Salemi R, Candido S, Falzone L, Santagati M, Stefani S, et al. Gut microbiota and cancer: from pathogenesis to therapy. Cancers. 2019;11(1):38. doi:10.3390/cancers11010038
27. Chen D, Wu J, Jin D, Wang B, Cao H. Fecal microbiota transplantation in cancer management: Current status and perspectives. Int J Cancer. 2019;145(8):2021-31. doi:10.1002/ijc.32003
28. Zhu Y, He C, Li X, Cai Y, Hu J, Liao Y, et al. Gut microbiota dysbiosis worsens the severity of acute pancreatitis in patients and mice. J Gastroenterol. 2019;54:347-58. doi:10.1007/s00535-018-1529-0
29. Zhang J, Xia Y, Sun J. Breast and gut microbiome in health and cancer. Genes Dis. 2021;8(5):581-9. doi:10.1016/j.gendis.2020.08.002
30. Matsukawa H, Iida N, Kitamura K, Terashima T, Seishima J, Makino I, et al. Dysbiotic gut microbiota in pancreatic cancer patients form correlation networks with the oral microbiota and prognostic factors. Am J Cancer Res. 2021;11(6):3163-75.
31. Okubo R, Kinoshita T, Katsumata N, Uezono Y, Xiao J, Matsuoka YJ. Impact of chemotherapy on the association between fear of cancer recurrence and the gut microbiota in breast cancer survivors. Brain Behav Immun. 2020; 85:186-91. doi:10.1016/j.bbi.2019.02.025
32. Laborda-Illanes A, Sanchez-Alcoholado L, Dominguez-Recio ME, Jimenez-Rodriguez B, Lavado R, Comino-Méndez I, et al. Breast and gut microbiota action mechanisms in breast cancer pathogenesis and treatment. Cancers. 2020;12(9):2465. doi:10.3390/cancers12092465
33. Sampsell K, Hao D, Reimer RA. The gut microbiota: a potential gateway to improved health outcomes in breast cancer treatment and survivorship. Int J Mol Sci. 2020;21(23):9239. doi:10.3390/ijms21239239
34. Xuan C, Shamonki JM, Chung A, DiNome ML, Chung M, Sieling PA, ET AL. Microbial dysbiosis is associated with human breast cancer. PloS One. 2014;9(1):e83744. doi:10.1371/journal.pone.0083744
35. Zhang X, Liu Q, Liao Q, Zhao Y. Pancreatic cancer, gut microbiota, and therapeutic efficacy. J Cancer. 2020;11(10):2749-58. doi:10.7150/jca.37445
36. Yang J, Yu J. The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. Protein Cell. 2018;9(5):474-87. doi:10.1007/s13238-018-0543-6
37. Terrisse S, Derosa L, Iebba V, Ghiringhelli F, Vaz-Luis I, Kroemer G, ET AL. Intestinal microbiota influences clinical outcome and side effects of early breast cancer treatment. Cell Death Differ. 2021;28(9):2778-96. doi:10.1038/s41418-021-00784-1
38. Ubachs J, Ziemons J, Soons Z, Aarnoutse R, van Dijk DP, Penders J, et al. Gut microbiota and short-chain fatty acid alterations in cachectic cancer patients. J Cachexia Sarcopenia Muscle. 2021;12(6):2007-21. doi:10.1002/jcsm.12804
39. Shen X, Li J, Li J, Zhang Y, Li X, Cui Y, et al. Fecal *enterotoxigenic Bacteroides fragilis–peptostreptococcus stomatis–parvimonas micra* biomarker for noninvasive diagnosis and prognosis of colorectal laterally spreading tumor. Front Oncol. 2021;11:661048. doi:10.3389/fonc.2021.661048
40. JRubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe. 2013;14(2):195-206. doi:10.1016/j.chom.2013.07.012
41. Cheng Y, Ling Z, Li L. The intestinal microbiota and colorectal cancer. Front Immunol. 2020;11:615056. doi:10.3389/fimmu.2020.615056
42. Khodaverdi N, Zeighami H, Jalilvand A, Haghi F, Hesami N. High frequency of enterotoxigenic *Bacteroides fragilis* and *Enterococcus faecalis* in the paraffin-embedded tissues of Iranian colorectal cancer patients. BMC Cancer. 2021;21(1):1353. doi:10.1186/s12885-021-09110-x
43. Abd Ellatif SA, Bouqellah NA, Abu-Serie MM, Razik ES, Al-Surhanee AA, Askary AE, et al. Assessment of probiotic efficacy and anticancer activities of *Lactiplantibacillus plantarum* ESSG1 (MZ683194. 1) and *Lactiplantibacillus pentosus* ESSG2 (MZ683195. 1) isolated from dairy products. Environ Sci Pollut Res. 2022;29(26):39684-701. doi:10.1007/s11356-022-18503 7-z
44. Bhukya KK, Bhukya B. Exploration of Antidiabetic, Cholesterol-Lowering, and Anticancer Upshot of Probiotic Bacterium *Pediococcus pentosaceus* OBK05 Strain of Buttermilk. Probiotics Antimicrob Proteins. 2022;15:1484-1500. doi:10.1007/s12602-022-10002-0
45. Alan Y, Savcı A, Koçpınar EF, Ertaş M. Postbiotic metabolites, antioxidant and anticancer activities of probiotic Leuconostoc pseudomesenteroides strains in natural pickles. Arch Microbiol. 2022;204(9):571. doi:10.1007/s00203-022-03180-6
46. Haghi F, Goli E, Mirzaei B, Zeighami H. The association between fecal enterotoxigenic *B. fragilis* with colorectal

cancer. BMC Cancer. 2019;19:879. doi:10.1186/s12885-019-6115-1
47. Vrakas S, Mountzouris KC, Michalopoulos G, Karamanolis G, Papatheodoridis G, Tzathas C, et al. Intestinal bacteria composition and translocation of bacteria in inflammatory bowel disease. PLoS One. 2017;12(1):e0170034. doi:10.1371/journal.pone.0170034
48. Akshintala VS, Talukdar R, Singh VK, Goggins M. The gut microbiome in pancreatic disease. Clin Gastroenterol Hepatol. 2019;17(2):290-5. doi:10.1016/j.cgh.2018.08.045
49. Kaji R, Kiyoshima-Shibata J, Tsujibe S, Nanno M, Shida K. Probiotic induction of interleukin-10 and interleukin-12 production by macrophages is modulated by co-stimulation with microbial components. J Dairy Sci. 2018;101(4):2838-41. doi:10.3168/jds.2017-13868
50. Delgado S, Sánchez B, Margolles A, Ruas-Madiedo P, Ruiz L. Molecules produced by probiotics and intestinal microorganisms with immunomodulatory activity. Nutrients. 2020;12(2):391. doi:10.3390/nu12020391
51. Meng Y, Li B, Jin D, Zhan M, Lu J, Huo G. Immunomodulatory activity of *Lactobacillus plantarum* KLDS1. 0318 in cyclophosphamide-treated mice. Food Nutr Res. 2018;62. doi:10.29219/fnr.v62.1296
52. Rajoka MS, Zhao H, Lu Y, Lian Z, Li N, Hussain N, et al. Anticancer potential against cervix cancer (HeLa) cell line of probiotic *Lactobacillus casei* and *Lactobacillus paracasei* strains isolated from human breast milk. Food Funct. 2018;9(5):2705-15. doi:10.1039/C8FO00547H
53. Eslami M, Yousefi B, Kokhaei P, Hemati M, Nejad ZR, Arabkari V, et al. Importance of probiotics in the prevention and treatment of colorectal cancer. J Cell Physiol. 2019;234(10):17127-43. doi:10.1002/jcp.28473
54. Azad MA, Sarker M, Wan D. Immunomodulatory effects of probiotics on cytokine profiles. Biomed Res Int. 2018;2018:8063647. doi:10.1155/2018/8063647
55. Dargahi N, Johnson J, Donkor O, Vasiljevic T, Apostolopoulos V. Immunomodulatory effects of probiotics: Can they be used to treat allergies and autoimmune diseases?. Maturitas. 2019;119:25-38. doi:10.1016/j.maturitas.2018.11.002
56. Jacouton E, Chain F, Sokol H, Langella P, Bermudez-Humaran LG. Probiotic strain *Lactobacillus casei* BL23 prevents colitis-associated colorectal cancer. Front Immunol. 2017;8:1553. doi:10.3389/fimmu.2017.01553
57. Delgado S, Sánchez B, Margolles A, Ruas-Madiedo P, Ruiz L. Molecules produced by probiotics and intestinal microorganisms with immunomodulatory activity. Nutrients. 2020;12(2):391. doi:10.3390/nu12020391
58. Breyner NM, Michon C, de Sousa CS, Vilas Boas PB, Chain F, Azevedo VA, et al. Microbial anti-inflammatory molecule (MAM) from *Faecalibacterium prausnitzii* shows a protective effect on DNBS and DSS-induced colitis model in mice through inhibition of NF-κB pathway. Front Microbiol. 2017;8:114. doi:10.3389/fmicb.2017.00114
59. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, Mazmanian SK. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011;332(6032):974-7. doi:10.1126/science.1206095
60. Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. Front Immunol. 2021;12:578386. doi:10.3389/fimmu.2021.578386
61. Mi H, Dong Y, Zhang B, Wang H, Peter CC, Gao P, et al. *Bifidobacterium* infantis ameliorates chemotherapy-induced intestinal mucositis via regulating T cell immunity in colorectal cancer rats. Cell Physiol Biochem. 2017;42(6):2330-41. doi:10.1159/000480005
62. Kahouli I, Tomaro-Duchesneau C, Prakash S. Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. J Med Microbiol. 2013;62(8):1107-23. doi:10.1099/jmm.0.048975-0
63. Yousefi B, Eslami M, Ghasemian A, Kokhaei P, Salek Farrokhi A, Darabi N. Probiotics importance and their immunomodulatory properties. J Cell Physiol. 2019;234(6):8008-18. doi:10.1002/jcp.27559
64. Ren D, Li C, Qin Y, Yin R, Du S, Liu H, et al. Evaluation of immunomodulatory activity of two potential probiotic Lactobacillus strains by *in vivo* tests. Anaerobe. 2015;35:22-7. doi:10.1016/j.anaerobe.2015.06.008
65. Ma EL, Choi YJ, Choi J, Pothoulakis C, Rhee SH, Im E. The anticancer effect of probiotic *Bacillus polyfermenticus* on human colon cancer cells is mediated through ErbB2 and ErbB3 inhibition. Int J Cancer. 2010;127(4):780-90. doi:10.1002/ijc.25011
66. Luerce TD, Gomes-Santos AC, Rocha CS, Moreira TG, Cruz DN, Lemos L, et al. Anti-inflammatory effects of Lactococcus lactis NCDO 2118 during the remission period of chemically induced colitis. Gut Pathog. 2014;6(1):33. doi:10.1186/1757-4749-6-33
67. Morshedi M, Hashemi R, Moazzen S, Sahebkar A, Hosseinifard ES. Immunomodulatory and anti-inflammatory effects of probiotics in multiple sclerosis: a systematic review. J Neuroinflammation. 2019;16(1):231. doi:10.1186/s12974-019-1611-4
68. Peters VB, Van De Steeg E, Van Bilsen J, Meijerink M. Mechanisms and immunomodulatory properties of pre- and probiotics. Benef Microbes. 2019;10(3):225-36. doi:10.3920/BM2018.0066
69. Liu WH, Yang CH, Lin CT, Li SW, Cheng WS, Jiang YP, et al. Genome architecture of *Lactobacillus plantarum* PS128, a probiotic strain with potential immunomodulatory activity. Gut Pathog. 2015;7(1):22. doi:10.1186/s13099-015-0068-y
70. Yan F, Cao H, Cover TL, Whitehead R, Washington MK, Polk DB. Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. Gastroenterology. 2007;132(2):562-75. doi:10.1053/j.gastro.2006.11.022
71. Lee DK, Jang S, Kim MJ, Kim JH, Chung MJ, Kim KJ, et al. Anti-proliferative effects of *Bifidobacterium* adolescentis SPM0212 extract on human colon cancer cell lines. BMC Cancer. 2008;8(1):310. doi:10.1186/1471-2407-8-310
72. Shang F, Jiang X, Wang H, Chen S, Wang X, Liu Y, et al. The inhibitory effects of probiotics on colon cancer cells: *In vitro* and *in vivo* studies. J Gastrointest Oncol. 2020;11(6):1224-32. doi:10.21037/jgo-20-573
73. Ulaganathan V, Kandiah M, Shariff ZM. A case-control study of the association between metabolic syndrome and colorectal cancer: a comparison of International Diabetes Federation, National Cholesterol Education Program Adults Treatment Panel III, and World Health Organization definitions. J Gastrointest Oncol. 2018;9(4):650-63. doi:10.21037/jgo.2018.04.01
74. Ng C, Li H, Wu WK, Wong SH, Yu J. Genomics and metagenomics of colorectal cancer. J Gastrointest Oncol. 2019;10(6):1164-70. doi:10.21037/jgo.2019.06.04
75. Zhang M, Fan X, Fang B, Zhu C, Zhu J, Ren F. Effects of *Lactobacillus salivarius* Ren on cancer prevention and intestinal microbiota in 1, 2-dimethylhydrazine-induced rat model. J Microbiol. 2015;53:398-405. doi:10.1007/s12275-015-5046-z
76. Thirabunyanon M, Boonprasom P, Niamsup P. Probiotic potential of lactic acid bacteria isolated from fermented dairy milks on antiproliferation of colon cancer cells.

Biotechnol Lett. 2009;31:571-6. doi:10.1007/s10529-008-9902-3
77. Rafter J. The effects of probiotics on colon cancer development. Nutr Res Rev. 2004;17(2):277-84. doi:10.1079/NRR200484
78. Fotiadis CI, Stoidis CN, Spyropoulos BG, Zografos ED. Role of probiotics, prebiotics and synbiotics in chemoprevention for colorectal cancer. World J Gastroenterol. 2008;14(42):6453-7. doi:10.3748/wjg.14.6453
79. Jewett A, Hume WR, Le H, Huynh TN, Han YW, Cheng G, et al. Induction of apoptotic cell death in peripheral blood mononuclear and polymorphonuclear cells by an oral bacterium, *Fusobacterium nucleatum*. Infect Immun. 2000;68(4):1893-8. doi:10.1128/iai.68.4.1893-1898.2000
80. Shenker BJ, Datar S. *Fusobacterium nucleatum* inhibits human T-cell activation by arresting cells in the mid-G1 phase of the cell cycle. Infect Immun. 1995;63(12):4830-6. doi:10.1128/iai.63.12.4830-4836.1995
81. Huynh T, Kapur RV, Kaplan CW, Cacalano N, Haake SK, Shi W, et al. The Role of Aggregation in *Fusobacterium nucleatum*–Induced Immune Cell Death. J Endod. 2011;37(11):1531-5. doi:10.1016/j.joen.2011.06.034
82. Fridman WH, Pagès F, Sautès-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. Nat Rev Cancer. 2012;12(4):298-306. doi:10.1038/nrc3245
83. Nosho K, Sukawa Y, Adachi Y, Ito M, Mitsuhashi K, Kurihara H, et al. Association of Fusobacterium nucleatum with immunity and molecular alterations in colorectal cancer. World J Gastroenterol. 2016;22(2):557-66. doi:10.3748/wjg.v22.i2.557
84. Compare D, Nardone G. The bacteria-hypothesis of colorectal cancer: pathogenetic and therapeutic implications. Transl Gastrointest Cancer. 2014;3(1):44-53. doi:10.3978/j.issn.2224-4778.2013.05.37
85. Kuugbee ED, Shang X, Gamallat Y, Bamba D, Awadasseid A, Suliman MA, et al. Structural change in microbiota by a probiotic cocktail enhances the gut barrier and reduces cancer via TLR2 signaling in a rat model of colon cancer. Dig Dis Sci. 2016;61:2908-20. doi:10.1007/s10620-016-4238-7
86. Dikeocha IJ, Al-Kabsi AM, Eid EE, Hussin S, Alshawsh MA. Probiotics supplementation in patients with colorectal cancer: A systematic review of randomized controlled trials. Nutr Rev. 2022;80(1):22-49. doi:10.1093/nutrit/nuab006
87. Momo CH, Mboussaah AD, Franɜois Zambou N, Shaiq MA. New pyran derivative with antioxidant and anticancer properties isolated from the probiotic *Lactobacillus plantarum* H24 strain. Nat Prod Res. 2022;36(4):909-17. doi:10.1080/14786419.2020.1849201
88. Sheng S, Fu Y, Pan N, Zhang H, Xiu L, Liang Y, et al. Novel exopolysaccharide derived from probiotic *Lactobacillus pantheris* TCP102 strain with immune-enhancing and anticancer activities. Front Microbiol. 2022;13:1015270.
89. Castven D, Fischer M, Becker D, Heinrich S, Andersen JB, Strand D, et al. Adverse genomic alterations and stemness features are induced by field cancerization in the microenvironment of hepatocellular carcinomas. Oncotarget. 2017;8(30):48688-700. doi:10.18632/oncotarget.16231
90. De Leblanc AD, Matar C, Perdigyn G. The application of probiotics in cancer. Br J Nutr. 2007;98(S1):S105-10. doi:10.1017/S0007114507839602
91. Temraz S, Nassar F, Kreidieh F, Mukherji D, Shamseddine A, Nasr R. Hepatocellular carcinoma immunotherapy and the potential influence of gut microbiome. Int J Mol Sci. 2021;22(15):7800. doi:10.3390/ijms22157800
92. Yu AQ, Li L. The potential role of probiotics in cancer prevention and treatment. Nutr Cancer. 2016;68(4):535-44. doi:10.1080/01635581.2016.1158300
93. Grajek W, Olejnik A, Sip A. Probiotics, prebiotics and antioxidants as functional foods. Acta Biochim Pol. 2005;52(3):665-71. doi:10.18388/abp.2005_3428
94. Heydari Z, Rahaie M, Alizadeh AM. Different anti-inflammatory effects of *Lactobacillus acidophilus* and *Bifidobactrum bifidioum* in hepatocellular carcinoma cancer mouse through impact on microRNAs and their target genes. J Nutr Intermed Metab. 2019;16:100096. doi:10.1016/j.jnim.2019.100096
95. Sharma V, Garg S, Aggarwal S. Probiotics and liver disease. Perm J. 2013;17(4):62-7. doi:10.7812/TPP/12-144
96. Dos Reis SA, da Conceiçro LL, Siqueira NP, Rosa DD, da Silva LL, Maria do Carmo GP. Review of the mechanisms of probiotic actions in the prevention of colorectal cancer. Nutr Res. 2017;37:1-9. doi:10.1016/j.nutres.2016.11.009
97. Li J, Sung CY, Lee N, Ni Y, PihlajamɅki J, Panagiotou G, et al. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc Natl Acad Sci USA. 2016;113(9):E1306-15. doi:10.1073/pnas.1518189113
98. Elshaer AM, El-Kharashi OA, Hamam GG, Nabih ES, Magdy YM, Abd El Samad AA. Involvement of TLR4/CXCL9/PREX-2 pathway in the development of hepatocellular carcinoma (HCC) and the promising role of early administration of lactobacillus plantarum in Wistar rats. Tissue Cell. 2019;60:38-47. doi:10.1016/j.tice.2019.07.010
99. Kumar M, Verma V, Nagpal R, Kumar A, Gautam SK, Behare PV, et al. Effect of probiotic fermented milk and chlorophyllin on gene expressions and genotoxicity during AFB1-induced hepatocellular carcinoma. Gene. 2011;490(1-2):54-9. doi:10.1016/j.gene.2011.09.003
100. Wan ML, El-Nezami H. Targeting gut microbiota in hepatocellular carcinoma: probiotics as a novel therapy. Hepatobiliary Surg Nutr. 2018;7(1):11-20. doi:10.21037/hbsn.2017.12.07
101. Maleki-Kakelar H, Dehghani J, Barzegari A, Barar J, Shirmohamadi M, Sadeghi J, et al. *Lactobacillus plantarum* induces apoptosis in gastric cancer cells via modulation of signaling pathways in *Helicobacter pylori*. BioImpacts. 2020;10(2):65-72. doi:10.34172/bi.2020.09
102. Homan M. Are probiotics useful in Helicobacter pylori eradication?. World J Gastroenterol. 2015;21(37):10644-53. doi:10.3748/wjg.v21.i37.10644
103. Borruel N, Casellas F, Antolín M, Llopis M, Carol M, Espíin E, et al. Effects of nonpathogenic bacteria on cytokine secretion by human intestinal mucosa. ACG. 2003;98(4):865-70. doi:10.1111/j.1572-0241.2003.07384.x
104. Goderska K, Agudo Pena S, Alarcon T. *Helicobacter pylori* treatment: antibiotics or probiotics. Applied microbiology and biotechnology. 2018;102:1-7. doi:10.1007/s00253-017-8535-7
105. Ruggiero P. Use of probiotics in the fight against Helicobacter pylori. World J Gastrointest Pathophysiol. 2014;5(4):384-91. doi:10.4291/wjgp.v5.i4.384
106. Rasouli BS, Ghadimi-Darsajini A, Nekouian R, Iragian GR. *In vitro* activity of probiotic *Lactobacillus reuteri* against gastric cancer progression by downregulation of urokinase plasminogen activator/urokinase plasminogen activator receptor gene expression. J Cancer Res Ther.

2017;13(2):246-51. doi:10.4103/0973-1482.204897
107. Chen YH, Tsai WH, Wu HY, Chen CY, Yeh WL, Chen YH, et al. Probiotic *Lactobacillus* spp. act against *Helicobacter pylori*-induced inflammation. Journal of clinical medicine. 2019;8(1):90. doi:10.3390/jcm8010090
108. Zhang J, Guo J, Li D, Chen M, Liu J, Feng C, et al. The efficacy and safety of *Clostridium butyricum* and *Bacillus coagulans* in *Helicobacter pylori* eradication treatment: An open-label, single-arm pilot study. Medicine. 2020;99(45):e22976. doi:10.1097/MD.0000000000022976
109. Hashemi-Khah MS, Arbab-Soleimani N, Forghanifard MM, Gholami O, Taheri S, Amoueian S. An *In vivo* study of *lactobacillus rhamnosus* (PTCC 1637) as a new therapeutic candidate in esophageal cancer. Biomed Res Int. 2022;2022:7607470. doi:10.1155/2022/7607470
110. Gronnier C, Collet D. New trends in esophageal cancer management. Cancers. 2021;13(12):3030. doi:10.3390/cancers13123030
111. Meves V, Behrens A, Pohl J. Diagnostics and early diagnosis of esophageal cancer. Viszeralmedizin. 2015;31(5):315-8. doi:10.1159/000439473
112. Elsherif SB, Andreou S, Virarkar M, Soule E, Gopireddy DR, Bhosale PR, et al. Role of precision imaging in esophageal cancer. J Thorac Dis. 2020;12(9):5159-73. doi:10.21037/jtd.2019.08.15
113. Motoori M, Yano M, Miyata H, Sugimura K, Saito T, Omori T, et al. Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients. Clin Nutr. 2017;36(1):93-9. doi:10.1016/j.clnu.2015.11.008
114. Xia C, Su J, Liu C, Mai Z, Yin S, Yang C, et al. Human microbiomes in cancer development and therapy. MedComm. 2023;4(2):e221. doi:10.1002/mco2.221
115. Deng Y, Tang D, Hou P, Shen W, Li H, Wang T, et al. Dysbiosis of gut microbiota in patients with esophageal cancer. Microb Pathog. 2021;150:104709. doi:10.1016/j.micpath.2020.104709
116. Zhang Y, Yu K, Chen H, Su Y, Zhu W. Caecal infusion of the short-chain fatty acid propionate affects the microbiota and expression of inflammatory cytokines in the colon in a fistula pig model. Microb Pathog. 2018;11(5):859-68. doi:10.1111/1751-7915.13282
117. Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity. 2014;40(1):128-39. doi:10.1016/j.immuni.2013.12.007
118. Chang CW, Liu CY, Lee HC, Huang YH, Li LH, Chiau JS, et al. *Lactobacillus casei* variety *rhamnosus* probiotic preventively attenuates 5-fluorouracil/oxaliplatin-induced intestinal injury in a syngeneic colorectal cancer model. Front Microbiol. 2018;9:983. doi:10.3389/fmicb.2018.00983
119. Lee JW, Shin JG, Kim EH, Kang HE, Yim IB, Kim JY, et al. Immunomodulatory and antitumor effects in vivo by the cytoplasmic fraction of *Lactobacillus casei* and *Bifidobacterium longum*. J Vet Sci. 2004;5(1):41-8. doi:10.4142/jvs.2004.5.1.41
120. Moghbeli M, Abbaszadegan MR, Golmakani E, Forghanifard MM. Correlation of Wnt and NOTCH pathways in esophageal squamous cell carcinoma. J Cell Commun Signal. 2016;10:129-35. doi:10.1007/s12079-016-0320-3
121. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108. doi:10.3322/canjclin.55.2.74
122. Espinosa-Sánchez A, Suárez-Martínez E, Sánchez-Díaz L, Carnero A. Therapeutic targeting of signaling pathways related to cancer stemness. Front Oncol. 2020;10:1533. doi:10.3389/fonc.2020.01533
123. He H, Shao X, Li Y, Gihu R, Xie H, Zhou J, et al. Targeting signaling pathway networks in several malignant tumors: progresses and challenges. Front Pharmacol. 2021;12:675675. doi:10.3389/fphar.2021.675675
124. Eslami-S Z, Majidzadeh-A K, Halvaei S, Babapirali F, Esmaeili R. Microbiome and breast cancer: new role for an ancient population. Front Oncol. 2020;10:120. doi:10.3389/fonc.2020.00120
125. Mendoza L. Potential effect of probiotics in the treatment of breast cancer. Oncol Rev. 2019;13(2):422. doi:10.4081/oncol.2019.422
126. Fooladi AA, Yazdi MH, Pourmand MR, Mirshafiey A, Hassan ZM, Azizi T, et al. Th1 cytokine production induced by *Lactobacillus acidophilus* in BALB/c mice bearing transplanted breast tumor. Jundishapur J Microbiol. 2015;8(4):e17354. doi:10.5812/jjm.8(4)2015.17354
127. Yazdi MH, Dallal MM, Hassan ZM, Holakuyee M, Amiri SA, Abolhassani M, et al. Oral administration of *Lactobacillus acidophilus* induces IL-12 production in spleen cell culture of BALB/c mice bearing transplanted breast tumour. Br J Nutr. 2010;104(2):227-32. doi:10.1017/S0007114510000516
128. Gadelle DA, Raibaud PI, Sacquet ED. beta-Glucuronidase activities of intestinal bacteria determined both *in vitro* and *in vivo* in gnotobiotic rats. Appl Environ Microbiol. 1985;49(3):682-5. doi:10.1128/aem.49.3.682-685.1985
129. Gloux K, Berteau O, El Oumami H, Béguet F, Leclerc M, Doré J. A metagenomic β-glucuronidase uncovers a core adaptive function of the human intestinal microbiome. Proc Natl Acad Sci USA. 2011;108(supplement_1):4539-46. doi:10.1073/pnas.1000066107
130. McIntosh FM, Maison N, Holtrop G, Young P, Stevens VJ, Ince J, et al. Phylogenetic distribution of genes encoding β-glucuronidase activity in human colonic bacteria and the impact of diet on faecal glycosidase activities. Environ Microbiol. 2012;14(8):1876-87. doi:10.1111/j.1462-2920.2012.02711.x
131. Hirayama K, Rafter J. The role of probiotic bacteria in cancer prevention. Microbes Infect. 2000;2(6):681-6. doi:10.1016/S1286-4579(00)00357-9
132. JKim PI, Jung MY, Chang YH, Kim S, Kim SJ, Park YH. Probiotic properties of *Lactobacillus* and *Bifidobacterium* strains isolated from porcine gastrointestinal tract. Appl Microbiol Biotechnol. 2007;74:1103-11. doi:10.1007/s00253-006-0741-7
133. Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V, Kumar P, Poddar D, Aggarwal PK, Henry CJ, Jain S. Cancer-preventing attributes of probiotics: an update. Int J Food Sci Nutr. 2010;61(5):473-96. doi:10.3109/09637480903455971
134. Reid G, Sanders ME, Gaskins HR, Gibson GR, Mercenier A, Rastall R, et al. New scientific paradigms for probiotics and prebiotics. J Clin Gastroenterol. 2003;37(2):105-18.
135. de Moreno de LeBlanc A, Matar C, LeBlanc N, Perdigyn G. Effects of milk fermented by Lactobacillus helveticus R389 on a murine breast cancer model. Breast Cancer Res. 2005;7:R477. doi:10.1186/bcr1032
136. Pakbin B, Dibazar SP, Allahyari S, Javadi M, Amani Z, Farasat A, et al. Anticancer properties of probiotic Saccharomyces boulardii supernatant on human breast cancer cells. Probiotics Antimicrob Proteins. 2022;14(6):1130-8. doi:10.1007/s12602-021-09756-w
137. Vinothkanna A, Sathiyanarayanan G, Rai AK, Mathivanan K, Saravanan K, Sudharsan K, et al. Exopolysaccharide

produced by probiotic *Bacillus albus* DM-15 isolated from ayurvedic fermented *dasamoolarishta*: Characterization, antioxidant, and anticancer activities. Front Microbiol. 2022;13:832109. doi:10.3389/fmicb.2022.832109
138. Yazdi MH, Mahdavi M, Kheradmand E, Shahverdi AR. The preventive oral supplementation of a selenium nanoparticle-enriched probiotic increases the immune response and lifespan of 4T1 breast cancer bearing mice. Arzneimittelforschung. 2012;62(11):525-31. doi:10.1055/s-0032-1323700
139. Yazdi MH, Mahdavi M, Setayesh N, Esfandyar M, Shahverdi AR. Selenium nanoparticle-enriched Lactobacillus brevis causes more efficient immune responses in vivo and reduces the liver metastasis in metastatic form of mouse breast cancer. DARU J Pharm Sci. 2013;21:33. doi:10.1186/2008-2231-21-3
140. Andolfi C, Bloodworth JC, Papachristos A, Sweis RF. The urinary microbiome and bladder cancer: susceptibility and immune responsiveness. Bladder Cancer. 2020;6(3):225-35. doi:10.3233/BLC-200277
141. Wang YC, Ku WC, Liu CY, Cheng YC, Chien CC, Chang KW, et al. Supplementation of probiotic *butyricicoccus pullicaecorum* mediates anticancer effect on bladder urothelial cells by regulating butyrate-responsive molecular signatures. Diagnostics. 2021;11(12):2270. doi:10.3390/diagnostics11122270
142. He C, Li B, Huang L, Teng C, Bao Y, Ren M, et al. Gut microbial composition changes in bladder cancer patients: A case-control study in Harbin, China. Asia Pac J Clin Nutr. 2020;29(2):395-403.
143. Enaud R, Prevel R, Ciarlo E, Beaufils F, Wieërs G, Guery B, et al. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Front Cell Infect Microbiol. 2020;10:9. doi:10.3389/fcimb.2020.00009
144. Seow SW, Rahmat JN, Mohamed AA, Mahendran R, Lee YK, Bay BH. *Lactobacillus* species is more cytotoxic to human bladder cancer cells than *Mycobacterium Bovis* (bacillus Calmette-Guerin). J Urol. 2002;168(5):2236-9. doi:10.1016/S0022-5347(05)64362-5
145. Kandasamy M, Bay BH, Lee YK, Mahendran R. Lactobacilli secreting a tumor antigen and IL15 activates neutrophils and dendritic cells and generates cytotoxic T lymphocytes against cancer cells. Cell Immunol. 2011;271(1):89-96. doi:10.1016/j.cellimm.2011.06.004
146. de Lima Fragelli BD, Camillo L, de Almeida Rodolpho JM, de Godoy KF, de Castro CA, Brassolatti P, et al. Antitumor effect of il-2 and trail proteins expressed by recombinant *salmonella* in murine bladder cancer cells. Cell Physiol Biochem. 2021;55:460-76. doi:10.33594/000000398
147. Zhang W, Yang F, Mao S, Wang R, Chen H, Ran Y, Liu S, et al. Bladder cancer-associated microbiota: Recent advances and future perspectives. Heliyon. 2023;9:e13012. doi:10.1016/j.heliyon.2023.e13012
148. Kandati K, Belagal P, Nannepaga JS, Viswanath B. Role of probiotics in the management of cervical cancer: An update. Clin Nutr ESPEN. 2022;48:5-16. doi:10.1016/j.clnesp.2022.02.017
149. Mei Z, Li D. The role of probiotics in vaginal health. Front Cell Infect Microbiol. 2022;12:963868. doi:10.3389/fcimb.2022.963868
150. Chase D, Goulder A, Zenhausern F, Monk B, Herbst-Kralovetz M. The vaginal and gastrointestinal microbiomes in gynecologic cancers: a review of applications in etiology, symptoms and treatment. Gynecol Oncol. 2015;138(1):190-200. doi:10.1016/j.ygyno.2015.04.036
151. Cha MK, Lee DK, An HM, Lee SW, Shin SH, Kwon JH, et al. Antiviral activity of Bifidobacterium adolescentis SPM1005-A on human papillomavirus type 16. BMC Med. 2012;10:72. doi:10.1186/1741-7015-10-72
152. Pourmollaei S, Barzegari A, Farshbaf-Khalili A, Nouri M, Fattahi A, Shahnazi M, et al. Anticancer effect of bacteria on cervical cancer: Molecular aspects and therapeutic implications. Life Sci. 2020;246:117413. doi:10.1016/j.lfs.2020.117413
153. Jahanshahi M, Maleki Dana P, Badehnoosh B, Asemi Z, Hallajzadeh J, Mansournia MA, et al. Anti-tumor activities of probiotics in cervical cancer. J Ovarian Res. 2020;13(1):68. doi:10.1186/s13048-020-00668-x
154. Fettweis JM, Brooks JP, Serrano MG, Sheth NU, Girerd PH, Edwards DJ, et al. Differences in vaginal microbiome in African American women versus women of European ancestry. Microbiology. 2014;160(10):2272-82. doi:10.1099/mic.0.081034-0
155. Hütt P, Lapp E, Stsepetova J, Smidt I, Taelma H, Borovkova N, et al. Characterisation of probiotic properties in human vaginal lactobacilli strains. Microb Ecol Health Dis. 2016;27(1):30484. doi:10.3402/mehd.v27.30484
156. Dallal MM, Yazdi MH, Holakuyee M, Hassan ZM, Abolhassani M, Mahdavi M. *Lactobacillus casei* ssp. *casei* induced Th1 cytokine profile and natural killer cells activity in invasive ductal carcinoma bearing mice. Iran J Allergy Asthma Immunol. 2012:183-9.
157. Matsuki T, Pйdron T, Regnault B, Mulet C, Hara T, Sansonetti PJ. Epithelial cell proliferation arrest induced by lactate and acetate from *Lactobacillus casei* and *Bifidobacterium breve*. PloS One. 2013;8(4):e63053. doi:10.1371/journal.pone.0063053
158. Li X, Wang H, Du X, Yu W, Jiang J, Geng Y, et al. Lactobacilli inhibit cervical cancer cell migration *in vitro* and reduce tumor burden *in vivo* through upregulation of E-cadherin. Oncol Rep. 2017;38(3):1561-8. doi:10.3892/or.2017.5791
159. Nowak A, Zakłos-Szyda M, Rosicka-Kaczmarek J, Motyl I. Anticancer potential of post-fermentation media and cell extracts of probiotic strains: An *In Vitro* Study. Cancers. 2022;14(7):1853. doi:10.3390/cancers14071853
160. Yin TQ, Ou-Yang X, Jiao FY, Huang LP, Tang XD, Ren BQ. *Pseudomonas aeruginosa* mannose-sensitive hemagglutinin inhibits proliferation and invasion via the PTEN/AKT pathway in HeLa cells. Oncotarget. 2016;7(24):37121-31. doi:10.18632/oncotarget.9467
161. Tiptiri-Kourpeti A, Spyridopoulou K, Santarmaki V, Aindelis G, Tompoulidou E, Lamprianidou EE, et al. *Lactobacillus casei* exerts anti-proliferative effects accompanied by apoptotic cell death and up-regulation of TRAIL in colon carcinoma cells. PloS One. 2016;11(2):e0147960. doi:10.1371/journal.pone.0147960
162. Fooladi AA, Yazdi MH, Pourmand MR, Mirshafiey A, Hassan ZM, Azizi T, et al. Th1 cytokine production induced by *Lactobacillus acidophilus* in BALB/c mice bearing transplanted breast tumor. Jundishapur J Microbiol. 2015;8(4):e17345. doi:10.5812/jjm.8(4)2015.17354
163. Yazdi MH, Dallal MM, Hassan ZM, Holakuyee M, Amiri SA, Abolhassani M, et al. Oral administration of *Lactobacillus acidophilus* induces IL-12 production in spleen cell culture of BALB/c mice bearing transplanted breast tumour. Br J Nutr. 2010;104(2):227-32. doi:10.1017/S0007114510000516
164. Kim PI, Jung MY, Chang YH, Kim S, Kim SJ, Park YH. Probiotic properties of *Lactobacillus* and *Bifidobacterium* strains isolated from porcine gastrointestinal tract.

Appl Microbiol Biotechnol. 2007;74:1103-11. doi:10.1007/s00253-006-0741-7
165. Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V, et al. Cancer-preventing attributes of probiotics: an update. Int J Food Sci Nutr. 2010;61(5):473-96. doi:10.3109/09637480903455971
166. Reid G, Sanders ME, Gaskins HR, Gibson GR, Mercenier A, Rastall R, et al. New scientific paradigms for probiotics and prebiotics. J Clin Gastroenterol. 2003;37(2):105-18.
167. Sharma P, Kaur S, Kaur R, Kaur M, Kaur S. Proteinaceous secretory metabolites of probiotic human commensal *Enterococcus hirae* 20c, E. *faecium* 12a and L12b as antiproliferative agents against cancer cell lines. Front Microbiol. 2018;9:948. doi:10.3389/fmicb.2018.00948