An Update on the Effects of Probiotics on Gastrointestinal Cancers

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Because of their increasing prevalence, gastrointestinal (GI) cancers are regarded as an important global health challenge. Microorganisms residing in the human GI tract, termed gut microbiota, encompass a large number of living organisms. The role of the gut in the regulation of the gut-mediated immune responses, metabolism, absorption of micro- and macronutrients and essential vitamins, and short-chain fatty acid production, and resistance to pathogens has been extensively investigated. In the past few decades, it has been shown that microbiota imbalance is associated with the susceptibility to various chronic disorders, such as obesity, irritable bowel syndrome, inflammatory bowel disease, asthma, rheumatoid arthritis, psychiatric disorders, and various types of cancer. Emerging evidence has shown that oral administration of various strains of probiotics can protect against cancer development. Furthermore, clinical investigations suggest that probiotic administration in cancer patients decreases the incidence of postoperative inflammation. The present review addresses the efficacy and underlying mechanisms of action of probiotics against GI cancers. The safety of the most commercial probiotic strains has been confirmed, and therefore these strains can be used as adjuvant or neo-adjuvant treatments for cancer prevention and improving the efficacy of therapeutic strategies. Nevertheless, well-designed clinical studies are still needed for a better understanding of the properties and mechanisms of action of probiotic strains in mitigating GI cancer development.

Keywords: probiotic, gastrointestinal disorders, cancer, pathology, therapy

INTRODUCTION

The incidence of gastrointestinal (GI) neoplasms is rapidly increasing globally (Ashrafizadeh et al., 2020; Pourhanifeh et al., 2020; Shafabakhsh et al., 2021). GI cancers are a complex set of heterogeneous diseases and disorders (Wang et al., 2021) and are classified into more frequent sporadic and rare inherited forms. Environmental and genetic risk factors can cooperatively alter normal tissue into a precursor or a premalignant injury, culminating in malignancy. While the
precise genetic mechanisms are somewhat understood in a tissue-type- and cell-type-specific context, many common aspects exist between GI cancers of heterogenous origin (Wang et al., 2021). Consistent with the advances made in developing new diagnostic and therapeutic approaches for GI cancers, several probiotic strains are being used as nutritional supplements.

Probiotics are a group of viable microorganisms including bacteria and yeasts that if consumed in sufficient amounts, may afford health benefits to the host (Ganguly et al., 2011; Tantajji et al., 2019a; Tantajii et al., 2019b; Alipour Nosrati et al., 2021; Davoodvandi et al., 2021). The major advantage of probiotic administration is its ability to maintain gut microbial homeostasis, reduce pathogenic microorganisms in the GI tract, and restores homeostasis of intestinal microorganisms (Floch et al., 2011; Butt and Eppliein, 2019). Moreover, by modulating microbiota and immune responses, decreasing bacterial translocation, promoting the function of the gut barrier, inducing anti-inflammatory properties, triggering anti-pathogenic activity, and decreasing tumor development and metastasis, probiotics might contribute to the prevention and treatment of GI cancers (Servin, 2004; Cotter et al., 2005; Javanmard et al., 2018). Considering the potential roles of Helicobacter pylori (H. pylori) in the initiation of colorectal (Teimoorian et al., 2018; Butt and Eppliein, 2019) and gastric cancers (Allarouk et al., 2019), the possible properties of probiotics against GI neoplasm in humans have been investigated in relation to their suppressive effects on H. pylori (Taremi et al., 2005; Sanders et al., 2013; Russo et al., 2014; Khoder et al., 2016; Rasouli et al., 2017). By triggering immune activity, probiotics, as functional dietary supplements, may mitigate neoplastic predisposition and development of GI cancers (Liong, 2008; Zuccotti et al., 2008; Kumar et al., 2010; De Preter et al., 2011; Zhang et al., 2011).

CLINICAL OVERVIEW ON GI NEOPLASMS

Carcinogenesis is a multistage process characterized by genetic mutations (Nowell, 1976; Yuasa, 2003; Vogelstein and Kinzler, 2004). In the past, initiation and progression of tumors were considered as distinct processes. A critical observation that led to the multistage hypothesis was that neoplasm was clonal, with each neoplastic cell originating from a single progenitor (Nowell, 1976; Cahill et al., 1999). This model implied that genetic mutations required for neoplastic transformation did not occur at once, but rather progressively. With each stage in this process, the transforming cell obtained a new mutation that promoted cell survival or proliferation.

A cell clone was developed with all of the necessary aspects for neoplastic transformation through evolution or natural selection. Selection is a critical element of this process because mutations are random events; thus, only rare mutations result in activation of cell survival and growth-promoting pathways or inactivation of apoptotic pathways or tumor suppressors (Ponder, 2001). These mutations impart a selective survival and growth dominance to that cell and its progeny. This leads to the expansion of that cell into a clonal population. Further mutations that occur in cells of that clonal population provide a few rare cells with new superiority. These daughter cells are subjected to an additional round of clonal expansion. This process continues, building on round after round of clonal expansion, till a mass is generated, and neoplastic transformation has taken place (Nowell, 1976; Cahill et al., 1999).

The specific number of somatically acquired gene mutations necessary for neoplastic transformation is dependent upon which genes and tissues are targeted. In common solid tumors, such as those derived from the colon or pancreas, an average of 33–66 genes displays subtle somatic mutations that would be expected to alter their protein products. About 95% of these mutations are single-base substitutions (such as C > G), whereas the remainder are deletions or insertions of one or a few bases (such as CTT > CT). Of the base substitutions, 90.7% result in missense changes, 7.6% result in nonsense changes, and 1.7% result in alterations of splice sites or untranslated regions immediately adjacent to the start and stop codons (Vogelstein et al., 2013).

Typically, benign dysplastic intermediates develop before GI neoplasm. Indeed, they do not originate from normal tissues directly, and the dysplastic lesions are characterized by their morphology and categorized based on certain pathological indicators (Said, 2012). For example, in the colon, the adenoma–carcinoma pattern shows this promotion from normal mucosa to invasive carcinoma via dysplastic intermediates. This pattern has been well supported by many pathological and animal studies (Kim and Lance, 1997; Lynch and Hoops, 2002).

The same multistep pattern from normal tissue via dysplastic intermediates to malignancy has been shown for human pancreatic, esophageal, and gastric cancers (Hruban et al., 2001; Yuasa, 2003; Hruban et al., 2004; Lin and Beermann, 2004). Cancer always emerges in a dysplastic precursor lesion that is histologically or grossly apparent. Current models have shown that the sequence of events prior to intestinal gastric cancer is as follows: atrophic gastritis, intestinal-metaplasia, and adenomas, which develop into carcinomas (Yuasa, 2003). Precursor lesions that lead to pancreatic cancer have been formally agreed upon, and the characteristics necessary for their classification have been established (Hruban et al., 2001; Hruban et al., 2004). These criteria classify the pancreatic lesions for both scientific and clinical uses.

The concept of cancer stem cells highlighted new perspectives in understanding this disease. Although it is tempting to explain tumor formation and metastasis by the presence of stem cells, after almost a decade of intense research, it seems that cancer stem cells fail to explain how neoplasia evolves. It seems most likely that this population of cells is not a defined group of cells resting in a niche and populating the tumor with amplifying cells, but rather, that few or maybe multiple cells within the tumor can function as cancer stem cells if induced, yet also revert to the state of a “normal” cancer cell. In general, cancer stem cells resulting from mutations in stem/progenitor cells most likely undergo uncontrolled proliferation (Li and Neaves, 2006; Abdul Khalek et al., 2010; Welte et al., 2010).

PROBIOTIC AND CANCER THERAPY

Advances have been made over the last century to develop anticancer drugs that lead to drastically reducing of the side effects of medications (Falzone et al., 2018). However, the
beneficial effects of probiotics on metabolic profiles and biomarkers of inflammation and oxidative stress were previously reported (Asemi et al., 2012a; Asemi et al., 2012b; Tajadadi-Ebrahimi et al., 2014; Bahmani et al., 2016). Modifying the intestinal microbiome with oral probiotics has been applied to decrease side effects associated with drugs. The adverse effects caused by anticancer treatments mainly include mucositis and diarrhea. Among the advantages of probiotics are their low cost and general safety (Rondanelli et al., 2017). Probiotic application in clinical practice has displayed a wide range of advantages, such as improving antibiotics and Clostridium difficile-related diarrhea and respiratory tract infections (Rondanelli et al., 2017). Populating the gut microbiota in cancer patients with probiotics re-establishes both the functionality and quantities of commensal bacteria, which are reduced after treatments (Zitvogel et al., 2018). Nonetheless, probiotic administration in several clinical trials has been shown to re-establish healthy intestinal microbiota composition and to diminish diarrhea and other treatment-related damages to the gut, such as mucositis (Mego et al., 2013). Consistently, Lactobacillus containing probiotics prevent diarrhea and mucositis in individuals, who received chemotherapy/radiotherapy for pelvic malignancy (Gianotti et al., 2010; Lalla et al., 2014).

The specific mechanism associated with the antitumor properties of probiotics remains unclear. Gut microbiota affect a variety of pathways, which are considered to play a central role in this process. Primarily, probiotic bacteria play an essential role in the preservation of homeostasis, thus maintaining sustainable physicochemical conditions in the colon. Reduced pH causing inter alia by the excessive presence of bile acids in feces may be a direct cytotoxic factor affecting colonic epithelium leading to colon carcinogenesis. Regarding their involvement in the modulation of the pH and bile acid profile, probiotic bacteria, such as L. acidophilus and B. bifidum, have shown efficacy in cancer prevention (Biasco et al., 1991; Bernstein et al., 2005; Jia et al., 2018).

Probiotic strains are also responsible for maintaining the balance between the quantity of other participants of natural intestinal microflora and their metabolic activity. Putrefactive bacteria, such as Escherichia coli and Clostridium perfringens, naturally present in the gut, have been proven to be involved in production of carcinogenic compounds using enzymes such as β-glucuronidase, azoreductase, and nitroreductase (Gorska et al., 2019).

Another cancer-preventing strategy involving probiotic bacteria, such as chiefly Lactobacillus and Bifidobacillus strains, has been linked to the binding and degradation of potential carcinogens. Mutagenic compounds associated with the increased risk of colon cancer are commonly found in unhealthy food, especially fried meat. Ingestion of the Lactobacillus strain by human volunteers alleviated the mutagenic effect of diet rich in cooked meat, which resulted in decreased urinary and fecal excretion of heterocyclic aromatic amines (HAAs) (Lidbeck et al., 1992; Hayatsu and Hayatsu, 1993; Gorska et al., 2019).

Many beneficial compounds produced and metabolized by gut microbiota have been demonstrated to play an essential role in maintaining homeostasis and suppressing carcinogenesis. A specific population of gut microbiota is dedicated to the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate as a result of the fermentation of fiber-rich prebiotics. Except for their principal function as an energy source, SCFAs have also been proven to act as signaling molecules affecting the immune system, cell death, and proliferation as well as intestinal hormone production and lipogenesis, which explains their crucial role in epithelial integrity maintenance (Garrett, 2015; Requena et al., 2018; Gorska et al., 2019).

Figure 1 shows both the advantages and potential disadvantages of probiotic administration as adjuvants during cancer treatments. The figure highlights show probiotics' regulation of the gut's subtle equilibrium, from microbial imbalance (dysbiotic) to functional and healthy microbiota.

**EFFECTS OF PROBIOTICS ON GASTROINTESTINAL CANCER CELLS**

**Probiotics and Gastric Cancer**

*H. pylori*-mediated inflammation is one of the potential factors in the induction of gastric cancer in infected populations (Moss, 2017). Evidence evaluating the anti-gastric cancer effects of probiotics has focused on *H. pylori*-induced pathophysiology of this type of cancer. Maleki-Kakelar and others reported that by mediating numerous molecular pathways, Lactobacillus plantarum (L. plantarum) caused significant inhibitory effects on the *H. pylori* growth rate. Upon downregulation of the AKT gene and upregulation of the phosphatase and tensin homolog (PTEN), Bcl-2–associated X (Bax), and toll-like receptor 4 (TLR4), L. plantarum significantly inhibited the proliferation of AGS and CRL-1739 human gastric cell lines (Maleki-Kakelar et al., 2020). Interleukin-8 (IL-8) is an inflammatory chemokine that plays critical roles in inflammatory pathways (Meniai et al., 2018). In the human gastric epithelial cell line-1 (GES-1), Lactobacillus bulgaricus (L. bulgaricus) inhibited the production of IL-8. In addition, Lactobacillus acidophilus (L. acidophilus) and L. bulgaricus inhibited adhesion of *H. Pylori* to GES-1 cells that attenuated inflammation in these cells (Song et al., 2019). Lin et al. reported that supplementation with Lactobacillus fermentum P2 (L. bacillus P2), L. casei L21, L. rhamnosus JB3, or their combination in *H. pylori*-infected mice reduced the expression level of interferon gamma (IFN-γ) along with interleukin-1 beta (IL-1β). Besides, *H. pylori* concentrations in the stomach of infected mice were decreased after probiotic supplementation (Lin et al., 2020). Another study demonstrated that L. acidophilus, L. plantarum, and L. rhamnosus supplementation significantly attenuated *H. pylori*-induced inflammation in vivo (Asgari et al., 2020). As mentioned earlier, most of the anti-gastric cancer studies have been directed at the inhibitory effects on *H. pylori* infection. Further experimental studies are needed for evaluating the effects of probiotic on gastric cancer inhibition mechanistically.

Ornithine decarboxylase is a crucial enzyme in the polyamine biosynthesis pathway and is responsible for catalyzing the decarboxylation of ornithine into putrescine (Svensson et al.,...
Ornithine decarboxylase is a neovascularization agent in tumoral cells and has been overexpressed in tumors of epithelial origin including colorectal, prostate, and gastric cancers (Ma et al., 2007). Russo and others demonstrated that treatment with *L. rhamnosus* GG homogenate and cytoplasm extracts significantly decreased the activity of ornithine decarboxylase, reducing the polyamine content of HGC-27 human gastric cancer cells. Furthermore, in comparison with the untreated control group, probiotic treatment considerably increased the ratio of Bax/Bcl-2 (Russo et al., 2007). Xie and others reported that 8-day postoperative probiotic supplementation in gastric cancer patients significantly reduced diarrhea occurrence. Furthermore, in probiotic-induced patients, the expression level of interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α) was significantly decreased compared with that in patients in the control group (Xie et al., 2018). Rasouli et al. reported that treatment with *Lactobacillus reuteri* (*L. reuteri*), in AGS gastric cancer cells, downregulated the expression level of the uPA/uPAR gene (Rasouli et al., 2017).

### FIGURE 1 | Risks and benefits of probiotics associated with cancer treatment. Schematic depiction of healthy gut microbiota in humans, occupied by symbiotic bacteria (top left box) against tumor-affected microbiota and dysbiosis of the gut (top right box). Anticancer treatment may negatively influence gut microbiota, leading to dysbiotic unbalance (bottom right square). Probiotic administration may re-adjust the dysbiotic conditions mediated by tumor growth and treatment. Probiotics may improve gastrointestinal therapy-related side effects, so they re-establish the intestinal symbiosis (bottom left square). The application of probiotics in anticancer therapy has benefits and risks (central bottom box).

Probiotics and Colon Cancer

Probiotics and Colon Cancer in Human Studies

One of the important goals in treating colorectal cancer patients is improving their quality of life. The role of probiotics in decreasing the symptoms and improving the quality of life in colorectal cancer patients has been evaluated at different stages of the disease. Lactofitol supplementation for 12 weeks in patients with colorectal cancer reduced the frequency of bowel symptoms while promoted functional well-being scores compared with those of patients in the placebo group (Lee et al., 2014). Zonulin (haptoglobin 2 precursor) is a regulator of tight junctions and intestinal permeability in the wall of the digestive tract (Sturgeon and Fasano, 2016). The increased serum level of zonulin was associated with autoimmunity, inflammatory diseases, and gastrointestinal cancers (Mörkl et al., 2018).
Supplementation for 16 days (6 preoperatively and 10 days postoperatively) with an admixture of *L. plantarum*, *L. acidophilus*-11, and *B. longum*-88 in colorectal cancer patients caused significant reduction in serum concentrations of zonulin as well as the duration of postoperative pyrexia, antibiotic therapy, and infectious complications in comparison with those in the placebo group. In addition, probiotic intervention inhibited the p38 mitogen-activated protein kinase signaling pathway (Liu et al., 2012). Yang and others reported that probiotic intervention with an admixture of *B. lactis* reduced the number of days to first defecation, days to first flatus, and diarrhea in the probiotic-treated group (Yang et al., 2016). 5-Fluorouracil (5-FU) is one of the most effective drugs for colorectal cancer proliferation (Zhou et al., 2018). Using an admixture of *B. longum*, *L. acidophilus*, and *Enterococcus faecalis* (*E. faecalis*) in colorectal cancer patients (*n* = 11) for 5 days significantly altered mucosa-associated microbiota of the intestine. Furthermore, probiotic intervention reduced the secretion of taxon assigned to the *Fusobacterium* (Gao et al., 2015). The treatment of colorectal cancer patients (*n* = 84) with a combination of probiotics, which consisted of *L. acidophilus*, *L. plantarum*, *B. lactis*, and *Saccharomyces boulardii* (1 day preoperatively and 15 days postoperatively), significantly decreased pneumonia, surgical site infections, anastomosis leakage, and need for mechanical ventilation compared with those who did not receive probiotic supplementation (Kotzampassi et al., 2015). Other studies evaluating the properties of probiotics in colorectal cancer patients are summarized in Table 2.

### Table 2: Probiotics and Gastric Cancer

| Cancer cell line | Probiotic agent | Probiotic concentration | Duration of the study | Effect(s) | Model | Sample (n) | Ref. |
|-----------------|----------------|-------------------------|-----------------------|-----------|-------|-----------|-----|
| AGS             | *Lactobacillus reuteri* | 1.5 × 10⁸ CFU/ml | 24, 48, and 72 h | Inhibited cell proliferation and decreased uPA and uPAR | In vitro | NA | Rasouli et al. (2017) |
| HGC-27          | *Lactobacillus paracasei* | 1 × 10⁸ CFU/ml | 24 or 48 h | Reduced the polyamine content and neoplastic proliferation | In vitro | NA | Orlando et al. (2012) |
| NCI-N87 and AGS | *Lactobacillus acidophilus* 74-2 and *Bifidobacterium lactis* 420 | 8.24 × 10⁷ and 2.20 × 10⁶ CFU, respectively | NA | Upregulated the expression of COX-1 | In vitro | NA | Markonen et al. (2008) |
| HGC-27          | *Lactobacillus rhamnosus* GG (ATCC 53103) | 1 × 10⁸ CFU/ml | 24 and 48 h | Reduced the polyamine content and neoplastic proliferation | In vitro | NA | Linsalata et al. (2010) |
| HGT-1           | *Propionibacterium freudenreichii* ITG P9 | 9 × 10¹⁵ CFU/ml | 24, 48, or 72 h | Induced caspase activation and cytochrome c release | In vitro | NA | Cousin et al. (2012) |
| AGS             | *Lactobacillus fermentum* UCO-979C and *Lactobacillus casei* Shirota | 1.5 × 10⁸ CFU/ml | 0-48 h | Inhibited urease activity of *H. pylori* | In vitro | NA | Salas-Jara et al. (2016) |
| AGS             | *Lactobacillus plantarum* SBL | NA | 12, 24, and 48 h | Induced anti-proliferative effects and apoptosis | In vitro | NA | Nami et al. (2014) |
| Postoperative patients with gastric cancer | NA | NA | 7–8 days | Decreased the expression of IL-6, IL-8, and TNF-α | Human | 70 | Xie et al. (2018) |
| Gastric cancer patients | *Bifidobacterium* | NA | 4 weeks | Decreased SIBO and symptoms of gastric cancer in the intervention group | Human | 112 | Liang et al. (2016) |

uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; COX-1, cyclooxygenase 1; H. pylori, *Helicobacter pylori*; IL-6, interleukin 6; IL-8, interleukin 8; TNF-α, tumor necrosis factor alpha; SIBO, small intestine bacterial overgrowth.
### TABLE 2 | Probiotics and colon cancer in human studies.

| Subject | Probiotic agent | Probiotic concentration | Duration of the study | Effect(s) | Sample (n) | Ref. |
|---------|----------------|-------------------------|-----------------------|-----------|------------|-----|
| Postoperative patients with colorectal cancer | Lactobacillus acidophilus LA-5, Lactobacillus plantarum, Bifidobacterium lactis BB-12, and Saccharomyces boulardii | $1.75 \times 10^9, 0.5 \times 10^9, 1.75 \times 10^9$, and $1.75 \times 10^9$ CFU per capsule, respectively | 16 days (1 day prior to operation and 15 days after operation) | Modulated the gene expression of SOCS3 and significantly decreased postoperative complications including mechanical ventilation, infections, and anastomotic leakage | 84 | Kotzampassi et al. (2015) |
| Colorectal cancer | Bifidobacterium lactis | $1 \times 10^9$ CFU/gr | 4 weeks | The amounts of IL-1β, IL-2, IL-12, and hs-CRP in the probiotic group was significantly lower than those in symbiotic and probiotic intervention groups | 19 | Worthley et al. (2009) |
| Perioperative patients with colorectal cancer | Bifidobacterium longum (BB536) and Lactobacillus johnsonii (La1) | $2 \times 10^7$ CFU/d and $2 \times 10^9$ CFU/d (two separate doses) | 8 days (3 days before operation and 5 days after operation) | The count of CD3, CD4, and CD8 in both of the intervention groups was greater than that in the placebo group | 11 and 10 | Gianotti et al. (2010) |
| Perioperative patients with colon cancer | Bifidobacterium bifidum | $1 \times 10^{10}$ CFU | 17 days (7 days before operation and 10 days after operation) | Surgical site infection in the probiotic group significantly decreased compared to that in the antibiotic group | 100 | Sadahiro et al. (2014) |
| Colorectal cancer | Bifidobacterium | NA | 4 weeks | Decreased the symptoms of colorectal cancer in the intervention group | 88 | Liang et al. (2016) |
| Colorectal cancer | Lactobacillus rhamnosus R0011 and Lactobacillus acidophilus R0052 | $2 \times 10^9$ CFU | 12 weeks | Attenuated bowel symptoms and improved quality of life in colorectal cancer subjects | 28 | Lee et al. (2014) |
| Perioperative patients with colorectal and colon cancer | Bacillus natto and Lactobacillus acidophilus | NA | 3 months | In the colonic group, defecation frequency, anal pain, and the Wexner score were significantly better than those in patients in the rectal cancer group | 77 | Ohigashi et al. (2011) |
| Perioperative patients with colorectal cancer | Enterococcus faecalis T11Q, Clostridium butyricum TO-A, and Bacillus mesentericus TO-A | 2 mg, 2 mg, and 10 mg, respectively, per each tablet | 6–30 days (3–15 days prior to and after the surgery) | Enhanced the immune responses and improved the intestinal microbial environment in the probiotic group | 75 | Aisu et al. (2015) |
| Healthy subjects | Bifidobacterium longum (BB536-y) | NA | 5 weeks | Inhibited colorectal carcinogenesis | 14 | Ohara and Suzutani, (2018) |
| Colorectal cancer | Lactobacillus acidophilus and Lactobacillus plantarum | NA | NA | Reduced the severity of colorectal cancer | 25 | Znatzadeh et al. (2018) |
| Perioperative patients with colorectal cancer | Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis | $0.21$ gr ($1 \times 10^9$ CFU/gr) in each capsule | 3 days before operation | Promoted the expression levels of IgG and sIgA, while diminished the IL-6 and CRP serum in the intervention group | 30 | Zhang et al. (2018) |
| Perioperative patients with colorectal cancer | Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium bifidum, Lactobacillus plantarum, and Bifidobacterium infantis | $3 \times 10^{10}$ CFU | 7 days before operation | Hospital stay duration in the probiotic-administered patients was shorter than that of the patients in the placebo group | 20 | Tan et al. (2016) |
| Colorectal cancer | Bifidobacterium longum, Lactobacillus acidophilus, and Enterococcus faecalis | $6 \times 10^7$ CFU | 5 days | Probiotic treatment altered the mucosal microbial flora | 11 | Gao et al. (2015) |
| Perioperative patients with colorectal cancer | Lactobacillus plantarum, Lactobacillus acidophilus, and Bifidobacterium longum | $2$ g/day in a concentration of $2.6 \times 10^{10}$ CFU | 16 days (6 days preoperatively and 10 days postoperatively) | Probiotic treatment upregulated the mucosal tight junction protein expression | 50 | Liu et al. (2011a) |
| Patients with colorectal tumors | Lactobacillus casei Shirota | $1 \times 10^{10}$ CFU/gr | 4 years | Occurrence of tumors much significantly decreased in \(\text{(Continued on following page)}\) | 99 | Ishikawa et al. (2005) |
mucositis (Mi et al., 2017). Ras-p21 is an oncoprotein and plays critical roles in the induction of different cancers (Banys-Paluchowski et al., 2018). In rats with azoxymethane-induced colorectal cancer, 

**TABLE 2** | (Continued) Probiotics and colon cancer in human studies.

| Subject                             | Probiotic agent                                                                 | Probiotic concentration | Duration of the study | Effect(s)                                                                 | Sample (n) | Ref.       |
|-------------------------------------|----------------------------------------------------------------------------------|-------------------------|-----------------------|--------------------------------------------------------------------------|------------|------------|
| Perioperative patients with colorectal cancer | *Bifidobacterium longum,* *Lactobacillus acidophilus,* and *Enterococcus faecalis* | ≥3 × 10^7 CFU/gr        | 12 days (5 days preoperatively and 7 days postoperatively) | The incidence of diarrhea in the probiotic group was lower than that in the placebo group | 30         | Yang et al. (2016) |
| Perioperative patients with colorectal cancer | *Lactobacillus plantarum,* *Lactobacillus acidophilus* 11, and *Bifidobacterium longum* 88 | 2.6 × 10^15 CFU         | 16 days (6 days preoperatively and 10 days postoperatively) | Treatment with the probiotic decreased the infection rate, serum zonulin concentration, and duration of antibiotic therapy | 75         | Liu et al. (2012) |
| Healthy subjects                    | *Lactobacillus rhamnosus* *LC705* and *Propionibacterium freudenreichii ssp. shermanii JS* | 4 × 10^10 CFU (2 × 10^10 CFU of each strain per day) | 4 weeks               | Probiotic supplementation decreased the activity of β-glucosidase         | 37         | Hatakka et al. (2008) |

SOCS3 suppressor of cytokine signaling 3; IL-1β, interleukin 1 beta; IL-2, interleukin 2; IL-12, interleukin 12; hs-CRP, high-sensitivity C-reactive protein; IgG, immunoglobulin G; sIgA, sensitive immunoglobulin A; CRP, C-reactive protein.

**FIGURE 2** | Physiological nonspecific mechanisms of probiotics for preventing and treating colorectal cancer (CRC). Probiotics produce short-chain fatty acid (SCFA) and mediate apoptotic and anti-proliferative reactions in CRC cells. Produced SCFAs by probiotics protect the intestinal tract by preventing the histone deacetylases (HDACs) and overexpression of mucins, including MUC1, MUC2, and MUC4. SCFAs activate 5’-adenosine monophosphate-activated protein kinase. This is a critical factor in keeping the hypoxia-inducible factor via SCFAs, which improves the epithelial duct’s survival and function. Probiotics elevate antimicrobial peptides, including defensin and (LL-37) cathelicidin, from the intestinal mucosal layer. These peptides protect them against bacterial inoculation and invasion. Probiotics inhibit enzymatic activity of pathogenic bacteria, including enzymes such as nitroreductase, β-glucuronidase, azoreductase, and β-glucosidase. They also decrease the production of carcinogenic agents. Probiotics inhibit carcinogenic agents (N-nitrous and heterocyclic aromatic amines [HCA]) by two mechanisms (deactivation and binding). They are potent mutagens and result in carcinogenic mutations in intestinal cells. Moreover, probiotics increase the antioxidant enzyme production and inactivate carcinogen-deactivating agents, including glutathione reductase, glutathione-S-transferase (GST), superoxide dismutase (SOD), glutathione peroxidase, and catalase (CAT), and decrease their adverse effects. Besides, probiotics eliminate the risk of CRC development due to metabolites that have effects on the cytochrome p450. This figure is adapted from Eslami et al., (2019).

mucositis (Mi et al., 2017). Ras-p21 is an oncoprotein and plays critical roles in the induction of different cancers (Banys-Paluchowski et al., 2018). In rats with azoxymethane-induced colorectal cancer, *Bifidobacterium longum* (*B. longum*) administration significantly suppressed the tumor volume, tumor incidence, cell proliferation, and the expression of ras-
p21 (Singh et al., 1997). Administration of *L. plantarum* and *L. rhamnosus* promoted the expression of anti-oxidant enzymes such as glutathione, superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, and glutathione-S-transferase in rats with 1,2-dimethylhydrazine-induced colorectal cancer. Furthermore, the treatment increased the concentrations of pro-apoptotic agents, such as p53, B-cell lymphoma 2 (Bcl-2), BCL2-associated X (Bax), caspase-9, and caspase-3, which are involved in the p53-mediated apoptotic pathway (Walia et al., 2018). Walia and others demonstrated that 16-week supplementation with *L. plantarum* and *L. rhamnosus* decreased the expression of cyclooxygenase-2 (COX-2). Therefore, it appears that suppressing COX-2 is a potential protective mechanism against colon cancer development, leading to decreased tumor volume and incidence (Walia et al., 2015). Ki-67 is a tumor proliferative marker that is associated with the upper proliferation rate in various types of cancers (Sun and Kaufman, 2018). An admixture of *L. fermentum* and *L. acidophilus* in the mouse model of colorectal cancer reduced tumor growth, survival, and proliferation and decreased the expression of Ki-67 compared with those of the placebo group. Concomitantly, probiotic supplementation had no significant effects on the expression of cleaved caspase-3, E-cadherin, and β-catenin in comparison with that of the other group (Kahouli et al., 2017). In the dimethylhydrazine-induced colon cancer model, the probiotic strain *L. rhamnosus* GG suppressed the expression of β-catenin, COX-2, and TNF-α. Moreover, probiotic supplementation upregulated the expression of pro-apoptotic proteins Bax, p53, and caspase 3 and downregulated the expression of Bcl-2 as an anti-apoptotic agent (Kumar et al., 2012). Agah and others compared the efficacy of *L. acidophilus* and *B. bifidum* probiotic strains against the azoxymethane-induced mouse model of colon cancer. The results showed that the colonic lesions incidence was decreased after probiotic intervention compared with that of the control group, and these effects were more potent for *L. acidophilus* than for *B. bifidum*. Serum concentrations of tumor markers CEA and CA19-9 were reduced after treatment with probiotics, while the expression of interferon gamma (IFN-γ), interleukin-10 (IL-10), and the count of CD4+ and CD8+ cells were upregulated upon intervention (Agah et al., 2019a). Wang et al. evaluated the efficacy of 12-week probiotic VSL#3 supplementation on azoxymethane/dextran sulfate sodium-induced colitis-associated carcinogenesis (1.5 × 10^9 CFU). Compared with that of the untreated group, probiotic supplementation downregulated the expression level of IL-6 and TNF-α in a considerable manner. Furthermore, probiotic intervention decreased the Oscillibacter and Lachnoclostridium genera, coupled with increased presence of *Bacillus* and Lactococcus genera in the fecal microbial composition of mice samples (Wang et al., 2018a). The c-Jun NH2-terminal kinase (JNK) is a major protein kinase which belongs to the MAPK signaling pathway and plays pivotal functions in the regulation of cell proliferation, cell death, apoptosis, and other features of cancerous cells (Wu et al., 2019). Considering its interfering role in different molecular pathways including NF-kB, JNK has binary roles in cancer development/progression (Tournier, 2013). By inhibiting the phosphorylation of glycogen synthase kinase 3 beta (GSK3β), JNK has suppressive effects on the expression of β-catenin (Hu et al., 2009). Ali et al. reported that *L. casei* probiotic supplementation in mice with 1,2-dimethylhydrazine-induced colon cancer significantly reduced the number of aberrant crypt foci compared with that in untreated animals. Furthermore, by upregulating the expression of phosphorylated JNK-1, *L. casei* regulated the expression of β-catenin and phosphorylated GSK3β, leading to significant protective effects against colon cancer (Ali et al., 2019). Sakatani and others have demonstrated that a *L. brevis*-derived polyphosphate significantly promoted the activation of the ERK signaling pathway, expression of cleaved PARP, and the ratio of cleaved PARP/PARP in SW620 colon cancer cells and mice bearing SW620 tumor xenografts. These changes led to increased apoptosis and inhibition of colon cancer growth (Sakatani et al., 2016a). By increasing the level of various inflammatory cytokines including IL-18, TNF-α, and TGF-β1, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome can trigger metastasis in colon and colorectal cancer samples (Shaima’s Hamarsheh, 2020). The results of a recent study demonstrated that probiotic supplementation with the *E. faecalis* strain caused inhibitory effects on the activation of caspase-1 and maturation of IL-1β in vivo. Furthermore, *E. faecalis* suppressed the activation of NLRP3 inflammasome, and thereby protected animals from intestinal inflammation in dextran sulfate-induced colitis-associated colorectal cancer (Chung et al., 2019a). Two-week intervention with *L. casei* in 1,2-dimethylhydrazine dihydrochloride-induced colon cancer in mice reduced the occurrence of chemical-induced aberrant crypt foci and the activity of ornithine decarboxylase. As noted previously, by promoting the polyamine metabolism in tumoral cells, ornithine decarboxylase is a pivotal function in the induction of cell proliferation. Hence, suppression of this enzyme in vivo diminished colon cancer growth and proliferation (Irecta-Najera et al., 2017a). Numerous investigations have demonstrated that the expression level of insulin-like growth factor-1 (IGF-1) and IGF-1 receptor (IGF-1R) in colorectal cancer patients is associated with poor prognosis, chemoresistance, and increased invasiveness features (Shiratsuchi et al., 2011; Vigneri et al., 2015). Valadez-Bustos and others demonstrated that probiotic intervention with *B. longum* BAA-999 in the colorectal murine model reduced the expression level and activity of IGF-1/IGF-1R in a considerable manner. Furthermore, after probiotic supplementation, the expression level of insulin-like growth factor-binding protein-3 (IGFBP3) was normalized. Overall, the noted alterations led to reduction in the tumor volume and size (Valadez-Bustos et al., 2019). In a comprehensive *in vivo* investigation, Jacouton and others found that by decreasing the expression grade of IL-22 as a pro-inflammatory cytokine and upregulating the expression of caspase-7, caspase-9, and Bik, probiotic treatment with *L. casei* BL23 had significant anti-proliferative effects in the azoxymethane-induced colorectal cancer model (O’Mahony et al., 2001). Table 3 provides a summary of *in vivo* investigations on the efficacy of probiotics in colorectal cancers.
TABLE 3 | Probiotics and colon cancer in animal studies.

| Probiotic agent | Probiotic concentration | Duration of the study | Effect(s)                                                                 | Ref. |
|----------------|-------------------------|-----------------------|---------------------------------------------------------------------------|------|
| *Bifidobacterium longum* BAA-999 | $8.992 \times 10^{10}$ CFU/ml | 16 weeks             | Regulated IGF-1, IGF-1R, and IGFBP3 protein expressions                    | Valadez-Bustos et al. (2019) |
| *VSL#3* | $1.5 \times 10^{9}$ CFU | 3 months (5 days weekly) | The level of TNF-α and IL-6 was reduced in colon tissue and tumor load after probiotic intervention | Wang et al. (2018b) |
| *VSL#3* | $10^{9}$ CFU daily | 18 weeks             | Altered the microbial composition                                          | Arthur et al. (2013) |
| *Lactobacillus casei* strain Shirota 2.1 | $2.1 \times 10^{10}$ | 8, 12, and 25 weeks | Significantly inhibited aberrant crypt foci and colon carcinogenesis         | Yamazaki et al. (2000) |
| *Lactobacillus fermentum* and *Lactobacillus plantarum* | $2 \times 10^{9}$ CFU/g and 2 $\times 10^{8}$ CFU/g | 21 days | Decreased the number of crypts in the mice and the activities of β-galactosidase and β-galactosidase activities. Besides, reduced the number of total coliforms | Asha and Gayathri, (2012) |
| *VSL#3* | $1.3 \times 10^{6}$ CFU | 44 days              | Protected against carcinogenesis through regulating the IL-6/STAT3 signaling pathway | Do et al. (2016) |
| *Saccharomyces boulardii* | $3 \times 10^{6}$ CFU/ml and 6 $\times 10^{5}$ CFU/ml | 9 weeks              | Suppressed HER-2, HER-3, IGF-1R, EGFR-Erk, and EGFR-Akt expression levels and intestinal tumor growth | Chen et al. (2009) |
| *Lactobacillus delbrueckii* subsp. *bulgaricus* and Streptococcus thermophilus | less than $1 \times 10^{2}$ CFU/ml | 5 months            | Reduced β-glucuronidase and nitroreductase activity                         | de Moreno de LeBlanc and Perdignon, (2005) |
| *Lactobacillus casei* ATCC 393 | $10^{6}$ CFU | 2 weeks             | Showed protective effects against omithine decarboxylase activities         | Inreta-Nájera et al. (2017b) |
| *Lactobacillus acidophilus* and *Lactobacillus rhamnosus GG* | $1 \times 10^{9}$ lactobacilli/0.1 ml | 18 weeks            | Caused decrease in Bcl-2 and K-ras and increase in Bax and p53 expression levels. Promoted Bax-mediated apoptosis in colon carcinogenesis | Sharaf et al. (2018) |
| *Lactobacillus rhamnosus* GG MTCC 1106, *Lactobacillus casei* MTCC 1423, *Lactobacillus plantarum* MTCC 1407 | $1 \times 10^{9}$ CFU | 7 weeks             | Probiotic administration decreased the activity of β-glucosidase             | Verma and Shukla, (2013) |
| *Lactobacillus casei* BL23 | $5 \times 10^{9}$ CFU/ml | 53 days              | Decreased the expression of IL-22 while increased the expression of caspase-7, -9, and Bık | Jacouton et al. (2017) |
| *Lactobacillus salivarius* ssp. *salivarius* UCC118 | NA | 16 weeks            | Reduced the number of fecal coliform and enterococci levels                | O’Mahony et al. (2001) |
| *Enterococcus faecium* CRL 183 | NA | 42 weeks            | Increased the immune response by promoting the expression of NO, IL-4, IFN-γ, and TNF-α | Siveri et al. (2008) |
| *Lactobacillus acidophilus* LaIK2 and *Bifidobacterium bifidum* Bb/K3 | $2 \times 10^{9}$ CFU/g of each strain (20 g) | 32 weeks | Probiotics decreased the pre-neoplastic lesions and PCNA expression level Promoted angiotatin, VDR, and alkaline sphingomyelinsae expression | Mohania et al. (2014) |
| *VSL#3* | $33 \times 10^{6}$ CFU/g | 115 days            | Alevated colitis through regulating CXCR2 signaling Modulated the activity of the NLRR3 inflammasome and ameliorated colitis-associated colorectal cancer | Appleyard et al. (2011) |
| *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* | $1 \times 10^{7}$ CFU of each strain (5 days) | 9 weeks             | Regulated IGF-1, IGF-1R, and IGFBP3 protein expressions                      | Mendes et al. (2018) |
| *B. bifidum* (Bla/016P/M) and *Lactobacillus acidophilus* | $1 \times 10^{7}$ CFU of each strain (5 days) | 10 days before tumor induction and 5 months after it | Reduced the expression of RANTES, etoxin, p-IKK, and TNF-α while increased IL-10 expression | Agah et al. (2019b) |
| *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacterium bifidum* | $0.6 \times 10^{6}$ CFU of each strain | 1 week             | Reduced the expression of VDR, NFkB-p65, COX-2, and TNF-α expression levels were decreased after probiotic intervention | Mendes et al. (2018) |
| *Lactobacillus salivarius* Ren | $5\times 10^{8}$ and 1 $\times 10^{10}$ CFU/kg | 2 weeks             | Prevented carcinogenesis by regulating the intestinal microflora            | Zhu et al. (2014) |
| *Lactobacillus rhamnosus* GG CGMCC 1.2134 | $1 \times 10^{9}$ CFU/1 ml | 25 weeks             | Reduced β-catenin, Bcl-2, NFkB-p65, COX-2, and TNF-α expression levels were decreased after probiotic intervention | Gamalliat et al. (2016) |
| *Lactobacillus plantarum* AS1 | $10^{9}$ CFU/ml | 26 weeks             | Had antioxidant-induced prevention of colon carcinogenesis                  | Kumar et al. (2012) |
### TABLE 3 | (Continued) Probiotics and colon cancer in animal studies.

| Probiotic agent                        | Probiotic concentration | Duration of the study | Effect(s)                                                                 | Ref.                    |
|---------------------------------------|-------------------------|-----------------------|---------------------------------------------------------------------------|-------------------------|
| Lactobacillus casei Zhang              | $4 \times 10^6$ CFU    | NA                    | Suppressed tumorigenesis through modulating various adiponectin-elevated signaling pathways | Zhang et al. (2017)     |
| Lactobacillus casei BL23 and Lactococcus lactis MG1363 | $1 \pm 0.4 \times 10^7$ CFU/mouse | 6 months             | Along with the modulation of regulatory T-cells, promoted the expression of IL-6, IL-17, IL-10, and TGF-$\beta$  | Lenoir et al. (2016)   |
| Bacillus subtilis-SKm (KFC11520P) and Lactococcus lactis-GAm (KFC11510P) | $10^6$ CFU/g of Bacillus subtilis-SKm and $10^6$ CFU/g of Lactococcus lactis-GAm | 4 weeks               | Probiotics decreased the expression of NOS, COX-2, and Bcl-2 while increased Bax, p21, and p33 expression levels | Jeong et al. (2012)    |
| VSL#3                                 | $333 \times 10^6$ CFU/g | 2 weeks               | Reduced the expression of TNF-$\alpha$, IL-1$\beta$, IL-6, IL-2, and COX-2 while increased IL-10 expression | Talero et al. (2015)    |
| Propionibacterium freudenreichii TL133 VSL#3 | $2 \times 10^{10}$ CFU/ml $1.2 \times 10^7$ bacteria per day | 18 days, 32 days      | Increased the induction of apoptosis and increased the expression of TNF-$\alpha$, angiotensin, IL-17, and PPAR-$\gamma$ | Lan et al. (2008)       |
| Lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis and both of them | $5 \times 10^6$ CFU/g and $5 \times 10^6$ CFU/g and both strains | 10 weeks              | Increased the expression of caspase-3 and decreased the expression of Bcl-2 | Lin et al. (2019)       |
| Lactobacillus acidophilus              | $10^{10}$ CFU/ml        | 12 weeks              | Adenomas have been reported to be decreased after probiotic administration | Urbanska et al. (2009)  |
| Streptococcus thermophilus CRL807 and Lactobacillus deburrecki subsp. bulgaricus CRL864 | NA                      | 5 days                | Prevented colitis and carcigenesis via modulating anti-inflammatory responses | Del Carmen et al. (2016) |
| Lactobacillus plantarum (AdF10) and Lactobacillus rhamnosus GG (LGG) VSL#3 | $1 \times 10^{10}$ CFU | 16 weeks              | Regulated COX-2 expression | Wala et al. (2015)     |
| Lactobacillus acidophilus              | $2 \times 10^8$ CFU/ml  | 1 month               | Diminished the severity of colitis and tumor growth | Chung et al. (2017)     |
| Lactobacillus plantarum (AdF10) and Lactobacillus rhamnosus GG (LGG) | $10^{12}$ CFU/ml        | 16 weeks              | Attenuated COX-2, NOS, and c-Myc expression levels | Deol et al. (2018)      |
| Lactobacillus acidophilus              | At least $50 \times 10^6$ CFU/g of strains | 12 weeks             | Had chemopreventive effects | Wala et al. (2018)      |
| Lactobacillus rhamnosus CLR2           | $1 \times 10^8$ CFU for 14 consecutive days, then $1 \times 10^9$ CFU for 3 weeks | 5 weeks               | Decreased the activity of $\beta$-glucosidase and $\beta$-glucuronidase along with the reduction in aberrant crypt foci counts | Desrouillères et al. (2015) |
| Streptococcus thermophilus CRL807, Streptococcus thermophilus CRL807, Streptococcus thermophilus CRL807, Lactococcus lactis subsp. cremoris MG1363, Lactococcus lactis subsp. cremoris MG1363, and Lactococcus lactis subsp. cremoris MG1363 Lactobacillus acidophilus (NCK 2025) | $1 \times 10^{10}$ CFU/ml | 6 months             | Exerted anti-tumorigenic properties via increasing antioxidant enzymes and IL-10 expression level | Del Carmen et al. (2017) |
| Lactobacillus acidophilus (Delvo Pro LA-1), Lactobacillus rhamnosus (GG), Bifidobacterium animalis (CSCC 1941), and Streptococcus thermophilus (DD145) Bifidobacterium longum | $5 \times 10^6$ CFU | 4 weeks               | Regulated inflammation and prevented colonic polyposis | Khazaie et al. (2012)   |
| Lactobacillus acidophilus (Delvo Pro LA-1), Lactobacillus rhamnosus (GG), Bifidobacterium animalis (CSCC 1941), and Streptococcus thermophilus (DD145) Bifidobacterium longum | $10^{10}$ CFU/g | 4 weeks               | Suppressed DMH-induced colon cancer in rats | McIntosh et al. (1999)  |
| Bifidobacterium adolescentis SPM2012 | NA                       | NA                    | Exerted anti-proliferative and anti-oxidative properties | Allen et al. (2015)     |
| Bifidobacterium adolescentis SPM2012 | $1 \times 10^8$ CFU | 3 weeks               | Inhibited activity of harmful enzymes and proliferation | Kim et al. (2008)       |

*IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor receptor 1; IGFBP3, insulin-like growth factor-binding protein 3; TNF-$\alpha$, tumor necrosis factor alpha; IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; HER-2, human epidermal growth factor receptor 2; HER-3, human epidermal growth factor receptor 3; EGFR, epidermal growth factor receptor; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X; IL-22, interleukin 22; Bik, Bcl-2-interacting killer; IL-4, interleukin 4; IFN-$\gamma$, interferon gamma; PCNA, proliferating cell nuclear antigen; CXCR2, CXC chemokine receptor 2; NLRP3, NLR family pyrin domain-containing 3; RANTES, regulated upon activation, normal T cell expressed, and presumably secreted; IL-10, interleukin 10; NF-$\kappa$B, nuclear factor kappa B; COX-2, cyclooxygenase 2; IL-17, interleukin 17; TGF-$\beta$, transforming growth factor beta; NOS, inducible nitric oxide synthase; IL-1$\beta$, interleukin 1 beta; PPAR-$\gamma$, peroxisome proliferator-activated receptor gamma.*
Probiotics and Colon Cancer in In Vitro Studies

As mentioned earlier, caspase-3 is a pro-apoptotic factor and its decreased expression is associated with the shortened survival time in various types of cancers (Vince et al., 2018). Bacillus coagulans (B. coagulans) Unique IS2 exerted anti-proliferative and pro-apoptotic properties in the COLO 205 human colon cancer cell line. By activating the p-53-mediated apoptotic pathway, treatment with probiotics increased the expression of BAX, activation of caspase-3, cleavage of poly (ADP-ribose) polymerase, and release of cytochrome C. Furthermore, B. coagulans reduced the mitochondrial membranal potential and Bcl2 expression level (Madempuddi and Kalle, 2017). Orlando and others reported that L. rhamnosus GG intervention in Caco-2, HT-29, and SW480 colon cancer cell lines upregulated the Bax/Bcl-2 ratio, increasing apoptosis in these cells (Orlando et al., 2016). The cyclin family is a group of cell cycle regulators. Their aberrant expression is associated with tumorigenesis (Wood and Endicott, 2018). Intervention with L. paracasei subsp. paracasei reduced the expressions of cyclin D1 and cyclin E1 X12 in HT-29 colon cancer cells. In addition, probiotic intervention upregulated the expression of p27 as a cyclin-dependent kinase (CDK) inhibitor (Huang et al., 2016). CDK inhibition represents a potential mechanism for suppressing over proliferation of cancer cells induced by aberrant regulation of the cyclin family (Sánchez-Martínez et al., 2019). PTEN (phosphatase and tensin homolog) has been demonstrated to be a prominent tumor suppressor gene, which plays critical roles in the dephosphorylation of phosphatidylinositol 3,4,5-trisphosphate (PIP3) (Di Cristofano et al., 1998). The additional evidence indicated that downregulation of PTEN is associated with increased tumor growth and survival. Therefore, targeting PTEN inhibitors is one of the most effective means for decreasing the tumor incidence, tumor volume, and tumor growth rate (Lee et al., 2019a). Sambrani et al. demonstrated, in HT-29 colon cancer cells, that treatment with Saccharomyces cerevisiae (S. cerevisiae) caused a significant upregulation in the expression of PTEN and caspase-3, while the expression levels of Bcl-XL and ReIA were markedly decreased after probiotic intervention (Sambrani et al., 2019). Pichia kudriavzevii AS-12 treatment showed considerable cytotoxic properties in HT-29 and Caco-2 cells compared with those in normal control cells. In addition, Pichia kudriavzevii upregulated the expression of pro-apoptotic agents including Caspase-9, caspase-3, -8, and -9, and BAX protein, while the expression of anti-apoptotic Bcl-2 was decreased after yeast probiotic treatment in mentioned cell lines (Saber et al., 2017). Bacillus polymyxa treatment reduced ErbB2, ErbB3, cyclin D1, and E2F-1 transcription factor in HT-29, DLD-1, and Caco-2 colon cancer cells. These changes led to the suppression of over proliferation of cancerous cells (Ma et al., 2010). In another study, Lee et al. investigated the anti-cancer effects of the B. adolescentis-derived butanol extract in Caco-2, HT-29, and SW480 colorectal cell lines. The results showed that the butanol extract significantly promoted the activation of macropheages and upregulated the production of TNF-α and nitric oxide in tumor cells. These changes led to the induction of cytotoxic and anti-proliferative properties against colorectal cancer (Lee et al., 2008). Survivin is an anti-apoptotic gene, which has been reported to have a crucial role in the inhibition of apoptosis and subsequent tumor growth, proliferation, metastases, and invasiveness in various types of cancer, especially in colorectal cancer (Hernandez et al., 2011). Tiptiri-Kourpeti et al. demonstrated that L. casei ATCC 393 administration (10^9 CFU/ml) in CT26 and HT29 colon carcinoma cells upregulated the expression of the ligand TRAIL, which was induced by TNF-mediated apoptosis. Furthermore, L. casei declined the level of survivin expression (Tiptiri-Kourpeti et al., 2016). By significantly decreasing the expression of Bcl-2 and remarkable up-regulation in the expression grade of pro-apoptotic agents Bak and Bax, probiotic intervention with L. paracasei K5 showed anti-proliferative effects in Caco-2 cells (Chondrou et al., 2018). In another investigation, Chen et al. reported that various strains of Lactobacillus genera in HT-29 colon cancer cells promoted the expression level of the Bax protein, while decreasing the expression of Bcl-2, leading to a notable increase in the Bax/Bcl-2 ratio. Furthermore, the increased lactate dehydrogenase activity and the ensuing degradation of the cell membrane of tumor cells were observed (Chen et al., 2017). A summary of mechanistic in vitro investigations on probiotics and colon cancer is summarized in Table 4.

Probiotics and Other Gastrointestinal Cancer

The mitogen-activated protein kinase (MAPK) signaling pathway has crucial roles in the induction of intracellular responses from extracellular signals in cells. Aberrant regulation of this pathway leads to numerous homeostatic and pathologic sequelae, such as cancer (Chapnick et al., 2011). In the KB oral cancer cell line, probiotic intervention with L. plantarum reduced the expression of MAPK and caused significant upregulation in the expression of PTEN signaling transduction (Asoudeh-Fard et al., 2017). Zhang and others evaluated the properties of Lactobacillus salivarius (L. salivarius) REN supplementation in an animal model of 4-nitroquinoline-1-oxide-induced oral cancer. By decreasing the expression level of COX-2 and proliferating cell nuclear antigen (PCNA), L. salivarius intervention had significant inhibitory effects on tumor growth of oral cancer (Zhang et al., 2013). Another study demonstrated that Acetobacter syzygii and L. acidophilus (PTCC 1643) probiotic strains caused significant cytotoxicity and inhibitory effects against the KB cancer cell line (Aghazadeh et al., 2017). Barrett’s esophagus is a pathological condition in which the lining of the distal esophagus is damaged due to the exposure of the esophagus to stomach acid. In this situation, squamous epithelium of the esophagus is replaced by columnar epithelium (Spechler, 2013). Barrett’s esophagus plays a critical role in the induction of esophageal cancer and acts as an important risk factor for development of esophageal cancer (Conteduca et al., 2012). Mozaffari Namin et al. reported that B. longum and L. acidophilus treatment of Barrett’s esophagus cell...
### TABLE 4 | Probiotics and colon cancer (in vitro).

| Cancer cell line | Probiotic agent | Probiotic concentration | Effect(s)                                                                 | Ref.                      |
|------------------|-----------------|-------------------------|--------------------------------------------------------------------------|--------------------------|
| SW620            | Lactobacillus brevis SBL8803 | NA                      | Via activating the Erk pathway and inhibiting tumor growth               | Sakatani et al. (2016b)  |
| SW620            | Lactobacillus delbruecki | NA                      | Through triggering the caspase 3-mediated pathway and decreasing Bcl-2 and caused apoptosis. Besides, MMP-9 was decreased after intervention | Zhou et al. (2014)       |
| SW742            | Bifidobacterium    | NA                      | Inhibited the growth of cancer cells                                     | Otte et al. (2008)       |
| SW742            | Bifidobacterium and Lactobacillus | NA                      | Prevented the development of colorectal cancer                            | Bahrani et al. (2019)    |
| Colo320 and SW480| Lactobacillus acidophilus, Escherichia coli, Nissle 1917, and the probiotic mixture VSL#3 | 1 x 10⁹ CFU/ml | Regulated the expression of COX-2                                        | Otte et al. (2008)       |
| SW480 and Caco-2 | Lactobacillus casei K11, Lactobacillus casei M5, Lactobacillus casei SB27, and Lactobacillus casei x 12 | 5 x 10⁶ CFU/ml | Induced apoptosis in human colon cancer cells and increased the ratio of Bax/Bcl2 Lactobacillus cell-free supernatant activated the intrinsic apoptosis pathway | Lee et al. (2019b)       |
| HCT-116, A549, MCF-7, and HepG2 | Lactobacillus plantarum 27 (NCDC 012), Lactobacillus casei (NCDC 297), and Lactobacillus brevis (NCDC 021) | NA | Exerted anti-proliferative activities. Inhibited activity of α-glucosidase and α-amylase | Mushtaq et al. (2019)    |
| HCT-116           | Lactobacillus plantarum 10⁷–10¹¹ CFU/ml | Decreased the expression of MMP-9 and increased protein levels of ZO-1 | Escamilla et al. (2012)         |
| HCT-116           | Pediococcus pentosaceus GS4 | 1.1 x 10⁹ CFU/ml | Downregulated NF-κB and p-Akt signaling pathways                         | Dubey et al. (2016)      |
| HCT-116           | Aspergillus sp    | NA                      | Exhibited anti-tumor properties                                           | Choi et al. (2011)       |
| HT-29, HCT-116, and Caco-2 | Bifidobacterium bifidum BGN4 | NA | Inhibited the growth of cancer cell lines                                | You et al. (2004)        |
| HT-29             | Lactobacillus casei K11, Lactobacillus casei M5, Lactobacillus casei SB27, and Lactobacillus casei x 12 | NA | Cell cycle arrest induced at the G0/G1 phase                            | Di et al. (2018)         |
| HT-29             | Lactobacillus casei K11, Lactobacillus casei M5, Lactobacillus casei SB27, and Lactobacillus casei x 12 | 5 x 10⁶ CFU/ml | Increased Bax expression and decreased the caspase 3, mutant p53, and IL-8 expression | Brandi et al. (2019)     |
| HT-29             | Enterococcus faecium YF5 | 1 x 10¹¹ CFU | Inhibited foodborne pathogens                                             | Tan et al. (2013)        |
| HT-29             | Lactobacillus acidophilus 145 and Bifidobacterium longum 913 | 10⁸ CFU/g | Increased oxidative-induced damage                                        | Oberreuther-Moschner et al. (2004) |
| Caco-2 and HT-29  | Lactobacillus rhamnosus MD 14 | NA | Showed anti-genotoxic and cytotoxic properties against colon cancer       | Sharma et al. (2019)     |
| HT-29             | Lactobacillus casei 01, Lactobacillus casei ATCC 393, Lactobacillus plantarum ATCC 14917, and Lactobacillus paracasei KS | 10⁷ CFU/ml | Exerted cytotoxic effects                                                  | Liu et al. (2011b)       |
| HT-29 and Caco-2  | VSL#3-Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, and Streptococcus thermophilus | NA | Caused a significant decrease in proliferation of cancer cells in a time- and dose-dependent manner | Mantzourani et al. (2019) |
| HT-29 and L-929   | Lactobacillus paracasei and Lactobacillus brevis | NA | Increased the expression of PPARγ | Ewaschuk et al. (2008) |
| HT-29             | Lactobacillus acidophilus 606 | NA | Induced apoptosis in cancer cells                                          | Mojibi et al. (2019)     |
| HT-29 and HCT-116 | Lactobacillus plantarum | NA | Exerted anti-tumor properties by inducing the expression of Bcl-2, GRP78, Bc-2, and Bak | Kim et al. (2010)        |
| HT-29 and HCT-116 | Lactobacillus plantarum | NA | Increased the activity of caspase-3 and suppressed the Wnt/β-catenin signaling pathway. Therefore, reversed chemoresistance and enhanced the therapeutic effect of 5-FU in colon cancer | Mirzaei et al. (2016)    |
| HT-29 and HCT-116 | Lactobacillus spp | 3 x 10⁶ CFU/ml | Down-regulated expression of IL-1β and TNF-α, c-fos and cjun transcripts were significantly upregulated after probiotic intervention | Shyu et al. (2014)       |

(Continued on following page)
lines downregulated the expression of CDX1 (caudal type homeobox 1), COX-2, TNF-α, and p53, while the expression level of IL-18 was enhanced after intervention of both probiotic strains (Mozaffari Namin et al., 2015). Table 5 provides a summary on the effectiveness of probiotics for oral, esophageal, and pancreatic cancer.

| Cancer cell line | Probiotic agent | Probiotic concentration | Effect (s) | Ref. |
|------------------|----------------|-------------------------|------------|-----|
| HT-29            | Lactobacillus paracasei subsp. paracasei MSL | $10^7$ CFU/ml | Via generating ROS production, inducing cell cycle arrest, and calreticulin translocation | Hu et al. (2015b) |
| HT-29            | Leuconostoc mesenteroides | NA | By regulating MAPK1, Bax, and caspase 3 and downregulation of Akt, NF-Kb, and Bcl-XL, promoted apoptosis. Besides, suppressed the expression of miRNA-21 and miRNA-200b | Zununi Vahed et al. (2017) |
| HT-29, Caco2, and HeLa | Propionibacterium acidipropionici strain CNR280, Propionibacterium freudenreichenii subsp. freudenreichenii strain ITG18, and Propionibacterium freudenreichenii subsp. shermanii strain SI41 | NA | Via short-chain fatty acids acting on the mitochondria, caused apoptosis in cancer cells | Jan et al. (2002) |
| HT-29 and HCT-116 | Propionibacterium freudenreichenii | NA | Induced apoptosis by increasing pro-apoptotic gene expression (TRAIL-R2/DR5) and decreasing FLIP and XIAP. | Cousin et al. (2016) |
| Caco-2           | Bifidobacterium animalis subsp. lactis DSM10140, Bifidobacterium longum subsp. longum DSM20097, and Bifidobacterium breve DSM20213 | >5.0 logs CFU/g | Caused remarkable cytotoxic activities | Ayyash et al. (2018) |
| Caco-2           | Lactobacillus rhamnosus and Bifidobacterium lactis | $10^9$ CFU/ml | Induced FAS-independent apoptosis and increased BAX translocation and release of cytochrome c and cleavage of caspase-3 and -9 | Altonsy et al. (2010) |
| Caco-2 and HT-29 | Lactobacillus plantarum A7 and Lactobacillus rhamnosus GG | NA | Decreased the growth rate of cancer cells | Sadeghi-Alibadi et al. (2014) |
| Caco-2 and Caco-2 | Escherichia coli Nissle 1917 | $25 \times 10^8$ CFU | Decreased ROS generation | Wang et al. (2015) |
| Caco-2           | Lactobacillus plantarum | NA | Upregulated the mRNA expression of HBD-2 and modulated the TLR-2 and IL-23 expression | Paolillo et al. (2009) |
| Caco-2           | Lactobacillus paracasei | $10^8$ CFU/ml | Inhibited the mRNA expression of CXCR4 | Nozari et al. (2019) |
| Caco-2           | Pediococcus pentosaceus FP3, Lactobacillus salivarius FP25, Lactobacillus salivarius FP36, and Enterococcus faecium FP51 | NA | Triggered the biosynthesis of short-chain fatty acids | Thirabunyanon and Hong Wittayakorn, (2013) |
| Caco-2 and Caco-2 | Enterococcus faecium RM11 and Lactobacillus fermentum RM28 | NA | Triggered anti-proliferative activities in colon cancer cells | Thirabunyanon et al. (2009) |
| Caco2, SKCO-1, SW620, and IEC-18 | Lactobacillus casei ATCC334 | NA | Suppressed colon cancer progression via affecting the JNK pathway | Konishi et al. (2016) |
| DLD-1            | Lactobacillus rhamnosus strain GG | $10^9$ CFU/ml | Exerted anti-proliferative effects | Orlando et al. (2009) |
| DLD-1            | Lactobacillus rhamnosus (Lr) KCTC 12202Bp | NA | Inhibited cell proliferation through affecting the p53-p21-cyclin B1/Cdk1 signaling pathway | An et al. (2019) |
| TC-1             | Lactobacillus casei BL23, Lactococcus lactis MG1363, and Lactococcus lactis NZ9000 | $1 \times 10^8$ CFU of each strain or recombinant | Probabilistic strain Lactobacillus casei BL23 caused IL-2-mediated anti-tumoral properties | Jacouton et al. (2018) |
| CT-26            | Lactobacillus casei variety rhamnosus (Lor35) | $1 \times 10^3$–$7$ CFU of the probiotics | Downregulated the expression of TNF-α and IL-6 | Chang et al. (2018) |
| CT-26            | Lactobacillus acidophilus NCFM | $1 \times 10^8$ CFU | Suppressed tumor growth in intestinal tissue | Chen et al. (2012) |
| MCF-7, HT-29, HeLa, HepG2, HL60, K562, and MCF-10A | Lactobacillus plantarum strains | NA | Caused anti-proliferative and pro-apoptotic effects against malignant cancer cells | Chua et al. (2019) |
| LS513            | Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC380R | $10^9$ CFU/ml | Via upregulating the caspase-3 protein and enhanced the pro-apoptotic capacity of the 5-FU. | Baldwin et al. (2010) |
**CONCLUSION**

Owing to their effects on different aspects of host health, probiotics have been demonstrated to be important tools in clinical medicine. Various investigations using a plethora of experimental models, including *in vitro*, animal models, and human clinical studies, have shown that by inducing anticarcinogenic properties, anti-mutagenic effects, producing short-chain fatty acids, activating the immune system of the hosts, inhibiting the bacteria-induced conversion of procarcinogens to carcinogens, and reducing intestinal pH (which results in reduced microbial activity), probiotics can assist in the prevention and treatment of gastrointestinal cancers. Nonetheless, to date, the benefits of probiotic strains as bio-therapeutic agents have not been adequately investigated against GI cancers. Moreover, the clinical efficacy of probiotics, especially on mortality, remains largely unexplored. Hence, more clinical studies with adequate follow-up durations are needed to obtain a clearer understanding on the potential utility of various strains and optimal doses for the administration of probiotics as pharmacological tools to combat GI cancers.

**AUTHOR CONTRIBUTIONS**

HM and AS involved in conception, design, statistical analysis and drafting of the manuscript. AD, FF, ZB, HF, MA-K, and MA contributed in data collection and manuscript drafting. All authors approved the final version for submission. MT, MG, ORT, and VT, critically revised the manuscript. All authors approved the new authorship changes.

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