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The Potential Role of Probiotics in Cancer Prevention and Treatment

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ABSTRACT

The human gut microbiota has a significant effect on many aspects of human physiology such as metabolism, nutrient absorption, and immune function. Imbalance of the microbiota has been implicated in many disorders including inflammatory bowel disease, obesity, asthma, psychiatric illnesses, and cancers. As a kind of functional foods, probiotics have been shown to play a protective role against cancer development in animal models. Clinical application of probiotics indicated that some probiotic strains could diminish the incidence of postoperative inflammation in cancer patients. Chemotherapy or radiotherapy-related diarrhea was relieved in patients who were administered oral probiotics. The present review summarizes the up-to-date studies on probiotic effects and the underlying mechanisms related to cancer. At present, it is commonly accepted that most commercial probiotic products are generally safe and can improve the health of the host. By modulating intestinal microbiota and immune response, some strains of probiotics can be used as an adjuvant for cancer prevention or/and treatment.

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Introduction

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (1). Most of the probiotic products currently available contain lactic acid bacteria (LAB) which belong to the genera *Lactobacillus* and *Bifidobacterium*. The direct benefit of probiotic consumption is to help the host with the maintenance of intestinal microbial balance, the decrease of potentially pathogenic gastrointestinal microorganisms, the improvement of bowel regularity, and the restoration of intestinal microbiota homeostasis in antibiotic-associated diarrhea (2). The beneficial effects of probiotics depend on the probiotic strains (3–6). Some probiotic strains influence the host activities by colonizing the intestinal tract (7), and the adhesion of LAB to the intestinal mucosa might be disease-specific (8). The preparation or composition of probiotic products might also be factors that contribute to different effects. There were reports that the viability and stability were required for some probiotics to be effective (9,10), while more studies demonstrated that both live and inactivated LAB had the similar beneficial effects (11–14). In some cases, synbiotics (combination of probiotics and prebiotics) and combination of two or more probiotics have a superior effect to a single probiotic strain (15).

In addition to the direct benefit of probiotics on the improvement of the host gut microbiota, several studies have shown potential for probiotics in cancer prevention and treatment through microbiota modulation, immune modulation, reduced bacterial translocation, enhanced gut barrier function, anti-inflammatory and antipathogenic activity, with effects on reducing tumor formation and metastasis. Several strains of *lactobacilli* showed antagonistic activities against gastric-cancer-related *Helicobacter pylori* (16–18). It is commonly known that persistent infection of high-risk human papillomavirus (HPV) is causally linked to the development of cervical cancer. In a study including 54 women, Verhoeven et al. indicated that a daily probiotic drink for 6 months enhanced the clearance of HPV and cervical cancer precursors (19). The administration of probiotics or synbiotics significantly decreased the activities of intestinal procarcinogen enzymes which was associated with colonic carcinogenesis in experimental animal models (20–22). Furthermore, LAB could affect the maturation of immune cells and their products not only in the gut but also in the systemic immune organs such as lymph node and spleen, resulting in the inhibition of tumor formation (23,24). These results suggest probiotics to be potential dietary supplements against neoplastic

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predisposition through extensive influence on both local and systemic immune processes of the host (25–29). The present review summarizes the up-to-date studies on the antitumor effects of probiotics and the underlying mechanisms, with an aim to promote the clinical trials and applications of probiotics for cancer prevention and/or treatment.

Anticancer effects of probiotics in cancer cells/cell lines

Substantial research using human cancer cells/cell lines has demonstrated that probiotics possess antiproliferative or proapoptotic activities in these cells, among which colonic cancer cells and gastric cancer cells were most commonly studied. According to the report by Lee et al., the cytoplasmic fractions of *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium longum* showed significant antitumor activities in some cancer cell lines (25). Studies by Russo et al. and Orlando et al. indicated the antiproliferative role of the cytoplasmic extracts from *Lactobacillus rhamnosus* strain GG (LGG) in both human gastric cancer cells and colonic cancer cells (30–32), while another probiotic product named *Bifidobacterium adolescentis* SPM0212 inhibited the proliferation of three human colon cancer cell lines including HT-29, SW 480, and Caco-2 (33). Other probiotic products or strains that exerted antitumor activities against human colon cancer cells included *Bacillus polyfermenticus* (34), *Lactobacillus acidophilus* 606 (35), LGG/Bb12 (36), and LGG/*Bifidobacterium animalis* subsp. *lactis* (37). In addition, Cousin et al. reported that fermented milk containing *Propionibacterium freudenreichii* enhanced the cytotoxicity of camptothecin that was used as a chemotherapeutic agent for gastric cancer (38). An in vitro study using human colorectal carcinoma cells demonstrated the inhibitory activity of probiotics against cell invasion (39).

Other studied cell types included cervical cancer cells (40), breast cancer cells (41), and myeloid leukemia cells (42). In Table 1 we summarized the antiproliferative role of probiotic strains and their products toward various cancer cells. Since in vitro studies using cell lines indicated that probiotics had proapoptotic effects on carcinoma cells (43–47), probiotics-based regimens might be used as an adjuvant treatment during anticancer chemotherapy.

Anticancer effects of probiotics in experimental models

To further investigate the anticancer effects of probiotics, researchers have conducted animal model experiments using rats and mice. The outcomes of most studies turned out to be encouraging and showed potential clinical applications. As indicated in Table 2, treatment with *Lactobacillus acidophilus, Butyrivibrio fibrisolvens, Bacillus polyfermenticus, Lactobacillus plantarum, Lactobacillus fermentum*, or combination of *L. acidophilus* and *Bifidobacterium bifidum* significantly inhibited the colonic cancer development in rats or mice injected with a carcinogen 1,2-dimethylhydrazine (DMH) (9,48–54). Oral administration of probiotics (*Lactobacillus casei, Clostridium butyricum*, combination of *Lactobacillus rhamnosus* and *Bifidobacterium lactis*, combination of *Lactobacillus acidophilus, Lactobacillus helveticus*, and *Bifidobacterium* spp., or combination of *Bifidobacterium lactis* and resistant starch) in rats decreased the incidence of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) and colon cancer (15,21,55–57), while administration of beetroot juice fermented by *Lactobacillus brevis* and *Lactobacillus paracasei* provided protection against ACF formation in N-nitroso-N-methylurea

Table 1. Antiproliferative or proapoptotic effects of probiotics on human cancer cells.

	Cancer cells derived from					
Probiotic strains /related products	Colon	Stomach	Breast	Cervix	Myeloid	Ref.
L. acidophilus L. casei/B. longum	√	√	ND	ND	√	25
LGG	ND	√	ND	ND	ND	30
LGG/ *L. paracasei*	√	√	ND	ND	ND	31, 32
B. adolescentis	√	ND	ND	ND	ND	33
B.P.	√	ND	ND	ND	ND	34
L. acidophilus	√	ND	ND	ND	ND	35
LGG/Bb12	√	ND	ND	ND	ND	36
LGG/*B. animalis* subsp. *lactis*	√	ND	ND	ND	ND	37
P. freudenreichii	ND	√	ND	ND	ND	38
B. adolescentis	ND	ND	ND	√	ND	40
L. acidophilus/L. crispatus	ND	ND	√	ND	ND	41
L. kefiri (P-IF)	ND	ND	ND	ND	√	42

ND = no data; *L. acidophilus* = *Lactobacillus acidophilus*; *L. casei* = *Lactobacillus casei*; *B. longum* = *Bifidobacterium longum*; LGG = *Lactobacillus rhamnosus* strain GG; B.P. = *Bacillus polyfermenticus*; Bb12 = *Bifidobacterium lactis* Bb12; *P. freudenreichii* = *Propionibacterium freudenreichii*.

Table 2. Preventative effects of probiotics on animal tumors induced by various agents.

Probiotics/Synbiotics	Carcinogen	Animal	Antitumor effects			Ref.
			ACF	CRC	Others	
L. acidophilus	DMH	Rat	ND	√	ND	48
B. fibrisolvens	DMH	Rat	√	ND	ND	9
B.P.	DMH	Rat	√	√	ND	49, 50
L. acidophilus	DMH	Rat	√	ND	ND	51
L. plantarum	DMH	Rat	ND	√	ND	52
L. fermentum/*L. plantarum*	DMH	Mouse	√	ND	ND	53
L. acidophilus/*B. bifidum*	DMH	Rat	√	ND	ND	54
L. casei	AOM	Rat	√	√	ND	55
B. lactis/ *L. rhamnosus*	AOM	Rat	√	√	ND	56
L. acidophilus/*L. helveticus*/*B.* spp.	AOM	Rat	√	√	ND	57
C. butyricum	AOM	Rat	√	ND	ND	21
B. lactis/RS	AOM	Rat	ND	√	ND	15
L. brevis/*L. paracasei*	MNU	Rat	√	ND	ND	58
L. acidophilus	None	ApcMin/+ mouse	ND	√	ND	59
S.B.	None	ApcMin/+ mouse	ND	√	ND	60
L. casei	PhIP	Rat	ND	ND	Breast	62
L. salivarius	4NQO	Rat	ND	ND	Mouth	63
LGG	UV	Mouse	ND	ND	Skin	66

ND = No data; *L. acidophilus* = *Lactobacillus acidophilus*; B.P. = *Bacillus polyfermenticus*; *B. fibrisolvens* = *Butyrivibrio fibrisolvens*; *L. plantarum* = *Lactobacillus plantarum*; *L. fermentum* = *Lactobacillus fermentum*; *L. casei* = *Lactobacillus casei*; *B. lactis* = *Bifidobacterium lactis*; *L. rhamnosus* = *Lactobacillus rhamnosus*; *L. helveticus* = *Lactobacillus helveticus*; *B.* spp. = *Bifidobacterium* spp.; *C. butyricum* = *Clostridium butyricum*; RS = resistant starch; S.B. = *Saccharomyces boulardii*; *L. salivarius* = *Lactobacillus salivarius*; DMH = 1,2-dimethylhydrazine; AOM = azoxymethane; MNU = N-Nitroso-N-methylurea; PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; 4NQO = 4-nitroquinoline 1-oxide; ACF = aberrant crypt foci; CRC = colorectal cancer.

(MNU)-treated rats (58). According to the reports by Urbanska et al. and Chen et al., either *Lactobacillus acidophilus* or *Saccharomyces boulardii* exhibited inhibitory role against colorectal tumorigenesis in a mouse model carrying a germline APC mutation (59,60). Administration of probiotics dramatically mitigated enteric dysbacteriosis, ameliorated intestinal inflammation, and decreased liver tumor growth, suggesting an optional avenue for therapeutic prevention of hepatocellular carcinoma development (61). Long-term consumption of *Lactobacillus casei* in combination with soymilk achieved a beneficial effect for breast cancer prevention in chemically treated rats (62), and *Lactobacillus salivarius* was proven to inhibit the incidence of 4-nitroquinoline 1-oxide (4NQO)-induced oral cancer in rats (63). In addition, probiotics provided adequate protection of animals against radiation, chemical, or UV-induced damages (64–66). Nevertheless, these results should be interpreted with caution because most of the tumors were induced by various chemical agents, which was quite different from the natural process of carcinogenesis.

Anticancer effects of probiotics in clinical trials

Clinical studies have shown that certain probiotics are useful in the control of various intestinal disorders, including viral diarrhea, chemotherapy/radiotherapy or antibiotic-associated diarrhea, and postoperative inflammatory diseases. In a study that included 206 patients receiving radiotherapeutic treatment, *L. rhamnosus* (Antibiophilus) relieved the gastrointestinal toxicity related to radiation (67), while another study demonstrated the effectiveness of *L. casei* DN-114 001 on stool consistency of patients submitted to pelvic radiotherapy (68). According to the report by Delia et al., administration of VSL#3 (a mixture of 8 probiotics) to patients who were undergoing pelvic radiotherapy prevented the occurrence and severity of diarrhea (69,70). Combination of *L. acidophilus* and *B. bifidum* (Infloran) also had significant benefits on the stool consistency and the reduction of radiation-induced diarrhea (71). Of the conventional therapies for cancers, chemotherapy might change the human gut microbiota, resulting in favor of the colonization with *Clostridium difficile* and *Enterococcus faecium* (72). In patients who were diagnosed with colorectal cancer and submitted to chemotherapy, LGG effectively reduced the frequency of severe diarrhea and abdominal discomfort (73), and enteral administration of *Bifidobacterium breve* strain Yakult improved the intestinal environments of patients who received chemotherapy for pediatric malignancies (74). In addition, substantial evidence demonstrated that perioperative administration of probiotics effectively reduced the postoperative infectious complications (75–81).

As for the preventative role of probiotics in tumor formation, El-Nezami et al. demonstrated that 5-wk supplementation of probiotics reduced the urinary excretion of aflatoxin B(1)-N(7)-guanine (AFB-N(7)-guanine), a marker for hepatocyte carcinogenesis (82), and synbiotic consumption for 12 wk significantly reduced colorectal cancer risk (83). It is generally considered that probiotic

supplementation can reduce the risk of breast cancer development in perimenopausal women. However, Bonorden et al. and Nettleton et al. reported that short-term soy and probiotic supplementation did not markedly affect the concentrations of reproductive hormones in these women (84,85). It seems that long-term consumption of probiotics is necessary to achieve chemopreventive effect on the neoplastic development. For example, Ishikawa et al. demonstrated that probiotics prevented atypia of colorectal tumors in patients who were administered *L. casei* for 4 yr (86). Three months of yogurt consumption did not enhance cell-mediated immune function in young women (87), while regular consumption of *L. casei* strain Shirota (LcS) and soy isoflavone since adolescence was inversely associated with the incidence of breast cancer in Japanese women (88).

Mechanisms through which probiotics exert their functions

Generally speaking, the probiotics mentioned above exert their antitumor roles through improvement of intestinal microbiota, degradation of potential carcinogens, modulation of gut-associated and systemic immune, and enhancement of local and systemic antioxidant activity (for a review, see Ref. 89). As discussed in more details in the following contents, the anticarcinogenic effect may not be attributable to a single mechanism but rather to a combination of events.

Effects on intestinal microbiota homeostasis and bacterial translocation

Increased proportion of colonic bacteria with pro-inflammatory characteristics has been implicated in neoplastic formation. Accumulating evidence supports the hypothesis that probiotics have preventative effects on colorectal carcinogenesis by improving the intestinal environment. Probiotic lactobacilli significantly reduced the prevalence of colon cancer by modification of enteric flora in mice (90), and administration of probiotics reduced the bacterial overgrowth and the bacterial translocation in adult Wistar rats after 80% gut resection (91). A study administering probiotics to goats indicated that the supplement was able to modify microflora balance by increasing the LAB and *Bifidobacterium* and reducing Enterobacteriaceae like *Salmonella*/*Shigella*, resulting in the decrease of fecal mutagen concentration and fecal putrescine (92). In human beings, administration of *Lactobacillus rhamnosus* LC705 together with *Propionibacterium freudenreichii* ssp. *shermanii* JS increased the fecal counts of lactobacilli and propionibacteria and decreased the activity of β-glucosidase (93), an essential part of the bacterial glycolytic enzymes that might contribute to the development of colon cancer by generating carcinogens (94). Enterotoxigenic *Bacteroides fragilis* (ETBF) is a bacterium that is associated with diarrheal disease, inflammatory bowel disease, and colorectal cancer. In a study containing 32 adults who were found to be carriers of ETBF, probiotic yogurt was demonstrated to be effective for decreasing the cell number of ETBF (95).

The protective effects on intestinal barrier or DNA damage of intestinal epithelium

One feature in the promotion stage of colorectal carcinogenesis is the disruption of tight junctions, leading to a loss of integrity across the intestinal barrier. Commane et al. indicated that the fermentation products of pro- and prebiotics prevented disruption of the intestinal epithelial barrier (96), while Ko et al. demonstrated that *L. plantarum* inhibited the decrease in transepithelial electrical resistance of Caco-2 cells (97). Administration of probiotic products to patients undergoing biliary drainage improved the intestinal permeability and attenuated the inflammatory response (98,99). In addition, probiotics were proven to decrease the mutagen-induced DNA damage or DNA adduct formation in the colonic epithelium (100–103). An in vitro study using rat intestinal epithelial cells showed the preventative role of probiotics against enterocyte apoptosis and loss of intestinal barrier function caused by 5-fluorouracil (5-FU) (104), while an in vivo study with rats demonstrated that combination of resistant starch and *B. lactis* facilitated the apoptotic response to carcinogen-induced DNA damage of the rat colorectal cells (105). With this point of view, probiotics exert their functions similar to the tumor suppressor protein p53, which triggers cell apoptosis when the DNA damage is at high levels (106).

Modulation of gut-associated and/or systemic immune functions

Up to now, studies on the immune-regulatory role of probiotics in human beings were very limited and the number of study subjects was very small. Takeda and Okumura reported that daily intake of *L. casei* for 3 wk provided a positive effect on natural killer (NK) cell activity of health volunteers (107), while supplementation of synbiotics containing LGG, *B. lactis*, and oligofructose for 12 wk showed little effects on the systemic immune system of colon cancer patients (108). On the contrary, considerable reports demonstrated that administration of probiotics (or synbiotics) significantly decreased the occurrence of colon cancers in animal models through immunomodulatory effects. As

Table 3. Immunomodulatory effects of probiotics as evidenced in animals or cell lines.

			Immune and inflammatory parameters				
Probiotic products	Subject	Agent	NK cells	T Cells	Macrophages	Mediators	Ref.
LcS	Rat	AOM	ND	↑	ND	ND	55
LcS	Mouse	3-MC	↑	ND	ND	ND	109
SCM-III	Rat	AOM	ND	↑	ND	ND	57
LABs	Mouse	None	↑	↑	ND	ND	25
SYN	Rat	AOM	↑	ND	ND	IL-10↑	110
L. helveticus	Mouse	None	ND	↑	ND	IL-10↑, IL-6↓	111
B. fibrisolvens	Mouse	DMH	↑	ND	ND	GUS↓	9
B. fibrisolvens	Mouse	3-MC	↑	ND	ND	IFN-γ↑	23
LGG	Caco-2	Flagellin	ND	ND	ND	IL-8↓	11
LcS	Mouse	LPS	ND	ND	ND	IL-6↓	118
L. acidophilus	Mouse	None	ND	ND	ND	IL-12↑	24
B. longum/L. gasseri	Mouse	DMH	ND	ND	↑	ND	115
VSL#3	Rat	TNBS	ND	ND	ND	Angiostatin↑ Alk-Smase↑	119
VSL#3	Mouse	None	ND	↑	ND	IL-17&TNF-α↑ Angiostatin↑	112
L. acidophilus	Mouse	None	ND	↑	ND	IFN-γ, IL-4&TGF-β↑	113
LGG	Mouse	UV	ND	↑	ND	IFN-γ↑	66
L. reuteri	Mouse	None	ND	↑	ND	ND	114
LGG	Caco-2 cells	5-FU	ND	ND	ND	TNF-α, IL-12&MCP-1↑	14

ND = no data; LcS = *Lactobacillus casei* strain Shirota; SCM-III = a probiotic mixture containing *L. acidophilus, L. helveticus*, and *B. lactis* spp. 420; LABs = lactic acid bacteria including *L. acidophilus, L. casei*, and *B. longum*; SYN = Synbiotics containing LGG, *B. lactis* Bb12 and oligofructose-enriched inulin; VSL#3 = a mixture of eight probiotic strains containing *Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus plantarum*, and *Streptococcus salivarius* subspecies *thermophilus;* AOM = azoxymethane; 3-MC = 3-methylcholanthrene; DMH = 1,2-dimethylhydrazine; LPS = lipopolysaccharide; TNBS = trinitrobenzene sulfonic acid; 5-FU = 5-fluorouracil; GUS = β-glucuronidase; IFN-γ = Interferon-γ; TNF-α = tumor necrosis factor-α; TGF-β = transforming growth factor-β; MCP-1 = monocyte chemotactic protein-1.

summarized in Table 3, the NK cell number or cell cytotoxicity were increased in rats or mice treated with probiotic products (9,23,25,109,110). In addition, the probiotic products enhanced the host immune functions by increasing the number of CD4/CD8-positive lymphocytes (25,55,57,66,111–114) or the phagocytic activity of macrophages (115).

Long-term colonic inflammation promotes carcinogenesis and histological abnormalities such as dysplasia, a precursor of colorectal adenomas. In a study using the immortalized polyclonal human colon carcinoma cell line Caco-2, *B. lactis* sp. 420 showed the potential anti-inflammatory and anticarcinogenic properties by modulating the host expression profiles of cyclooxygenases (116), while another study using the mouse model demonstrated that probiotics increased the production of conjugated linoleic acids possessing anti-inflammatory and anticarcinogenic properties (117). More importantly, probiotics showed anti-inflammatory activities through regulating the production of inflammatory mediators such as interleukins, interferons, and cytokines (9,11,14,23,24,66,109–112,118,119), resulting in

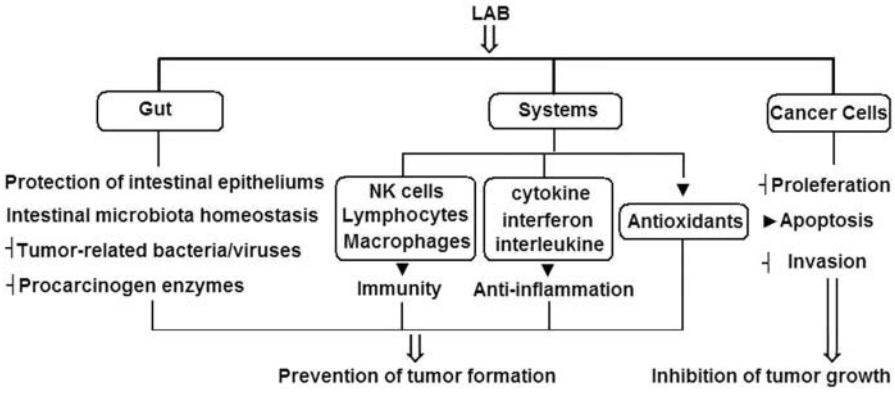

Figure 1. Illustration for the suppressive effects of probiotics on tumor formation and growth. Probiotics can exert their functions locally and systemically. Oral administration of probiotics can provide protection of intestinal epitheliums, modulate the homeostasis of the intestinal microflora, and inhibit the potential pathogens and carcinogenesis in the gut (⊣). Together with the enhancement of antioxidant activities (▼), probiotics can increase the number/activity of immune cells (▼) and control the inflammatory reaction, resulting in the prevention of tumor formation. In addition, probiotics can act on cancer cells by promoting cell apoptosis (►) and inhibiting cell proliferation or invasion (⊣), resulting in the suppression of tumor growth.

the effective control of inflammation and carcinogenesis. From Table 3 we can conclude that the probiotics regulate more than one indicator of the host immunity/inflammation in many cases.

In addition, there are isolated reports citing that administration of LAB results in increased activity of antioxidative enzymes (49,52,120), which provided beneficial effects on gut-associated and/or systemic antioxidant defense against carcinogen-induced damage.

Conclusion and perspectives

Probiotics have obtained increasing medical importance because of their beneficial effects upon the host health. As illustrated in Figure 1, oral administration of probiotics has multiple effects such as normalization of the intestinal microflora, improvement of the gastrointestinal barrier, and inhibition of potential pathogens or carcinogenesis in the gut. Together with the enhancement of systemic immune or/and anti-inflammatory activities, probiotics may play a part in the suppression of tumor formation and growth.

While laboratory-based studies have demonstrated encouraging outcomes that probiotics or synbiotics possess antitumor effects, the benefits should not be exaggerated before we get more results from human subjects. Randomized double-blind, placebo-controlled clinical trials should be done to gain the acceptance of the broader medical community and to explore the potential of probiotics as an alternative therapy for cancer control.

Author contribution statement

Ai-Qun Yu and Lianqin Li contributed equally to this work.

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