Cancer Chemopreventive Effects of Lactic Acid Bacteria

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Abstract Lactic acid bacteria (LAB) provide several potential health and nutritional benefits, including improving the nutritional value of food, controlling serum cholesterol levels, and controlling some types of cancer. Numerous in vitro, in vivo, human, and epidemiological studies have provided evidence of the chemopreventive effects of LAB on colon, bladder, liver, breast, and gastric cancers. These effects act via diverse mechanisms, including alteration of the gastrointestinal microflora, enhancement of the host’s immune response, and antioxidant and antiproliferative activities. This review discusses the recent progresses on the chemopreventive effects of LAB on specific cancer types and the underlying molecular mechanisms.

Keywords: Lactic acid bacteria, cancer, chemoprevention

Cancer is one of the leading causes of death worldwide [83], and carcinogenesis has been the subject of intense experimental, epidemiological, and clinical researches at the molecular, cellular, tissue, and clinical levels during the past two decades. However, the overall mortality rates of cancer have not declined significantly [53], and this has prompted a recent focus on reducing its incidence and the associated mortality rates. Because many human cancers are caused from preventable factors, such as infection, inflammation, smoking, and diet, preventive strategies might be the most effective to reduce cancers [52]. A proper diet may be one of the critical strategies for reducing the risk of cancer, with high consumptions of fruits and vegetables [85].

Lactic acid bacteria (LAB) have been shown to be an effective chemopreventive food ingredient against many cancer types. Over at least 4,000 years, LAB have been used to ferment foods such as cheese, yoghurt, and kimchi [18, 49, 51, 65]. LAB are described as Gram-positive, nonsporing, nonrespiring cocci or rods that produce lactic acid as the major end product during the fermentation of carbohydrates. The most common LAB genera in food fermentations are Carnobacterium, Enterococcus, Lactobacillus (Leb), Lactococcus (Lec), Leuconostoc (Leu), Oenococcus, Pediococcus, Streptococcus (S), Tetrarogenococcus, and Weissella. The genus Bifidobacterium (Bif) is unrelated to LAB phylogenetically, and Bifidobacterium species use a unique metabolic pathway for sugar metabolism. However, Bifidobacterium species are often considered to be LAB because they play a probiotic action by living in the gastrointestinal tract of humans and animals [84].

LAB provide several potential health and nutritional benefits, including improving the nutritional value of food, controlling gastrointestinal infections, improving digestion of lactose, controlling serum cholesterol levels, and controlling some types of cancer. These health benefits derive from a diverse range of biological activities and mechanisms [55]. This review focuses on the health-promoting benefits of LAB related to cancer prevention, the recent literature on the effects of LAB on specific cancer types, and the molecular components that underlie these effects.

CANCER-PREVENTIVE EFFECTS OF LAB ON SPECIFIC CANCER TYPES

Colorectal Cancer
Colorectal cancer is the second leading cause of cancer deaths in the United States for men and women combined. The increasing popularity of the Western meat-rich diet in Korea has increased the risk of colorectal cancer among Koreans [35]. Most researches that have investigated the relationship between LAB and cancer have concentrated on colorectal cancer. Bifidobacterium species decrease the growth rate and increase differentiation by increasing the activity of differentiation-related enzymes such as dipeptidyl peptidase IV and alkaline phosphatase in the HT-29 human colon adenocarcinoma cell line [5]. Fecal water from a
healthy male who received *Lcb. plantarum* treatments exhibited significantly reduced DNA damage in the HT-29 human colon adenocarcinoma cell line [7]. In our laboratory, the cytoplasmic fraction of *Lcc. lactis* ssp. *lactis* inhibited the proliferation of the SNUC2A human colon cancer cell line by inducing S-phase cell-cycle arrest [39].

In most in vivo studies, the anticancer effects of LAB have been evaluated in models in which colon cancer was chemically induced. Kulkarni and Reddy [45] reported that azoxymethane induced colonic aberrant crypts in male F344 rats fed a high-fat diet, whereas a group fed with lypoilized cultures of *Bifidobacterium* species showed 50% reduced rate compared with a control group. Rowland et al. [75] suggested that this result was due to a decrease in the β-glucuronidase activity and ammonia concentration in the rat feces. Singh et al. [82] also showed that the RAS mutation and ornithine decarboxylase activity decreased. Reddy and Rivenson [73] demonstrated the effects of *Bif. longum* on 2-amino-3-methylimidazo[4,5-f]quinoline (IQ)-induced colon carcinogenesis: F344 rats exposed to 0% and 0.5% lypoilized cultures of *Bif. longum* with 125 ppm IQ for 58 weeks exhibited a significantly lower incidence of colorectal tumors. 1,2-Dimethylhydrazine (DMH) also induces colon carcinogenesis, and *Lcb. acidophilius* reduced the incidence of colon tumors in DMH-treated F344 rats by 48% compared with a DMH-only group [20]. Fujino [16] also demonstrated that the incidence of colon tumors was reduced by 24% in DMH-treated mice that received a dietary supplement containing several LAB cultures compared with a DMH-only group.

In clinical tests, the number of *Bifidobacterium* species was significantly reduced in the fecal intestinal flora of patients with colon adenoma [44]. The administration of *Lcb. casei* can prevent the development of colorectal cancer, with a daily intake of live *Lcb. casei* suppressing atypia of colorectal tumors in 398 men and women who were free from tumors and who had had at least two colorectal tumors removed [29]. Rafier et al. [72] performed a 12-week randomized, double-blind, placebo-controlled trial of a foodstuff containing inulin, *Lcb. rhamnosus* GG, and *Bif. lactis* Bb12 in 37 colon cancer patients and 43 polypectomized patients. They found that fecal flora exhibited increased *Bifidobacterium* and *Lactobacillus* species and decreased *Clostridium* (C) *perfringens*. Colorectal proliferation and fecal-water-induced DNA damage of HT-29 human colon cancer cells were decreased. Moreover, epithelial barrier function was improved in polypectomized patients.

**Bladder Cancer**

The bladder is the fourth leading cancer-affected organ among men in the United States (after prostate, lung, and colon cancers) [30]. Smoking, working in rubber, chemical, and leather industries, and chronic bladder infection are the main causes of this type of cancer. The incidence of bladder cancer is nearly four times higher in men than in women, which may be attributable to the gender difference in the smoking rate [79]. This type of cancer is relatively easy to treat, but also frequently recurs and regrows more malignantly [87].

Seow et al. [80] demonstrated the antiproliferative activities of two types of lactobacilli on two bladder cancer cell lines: both *Lcb. rhamnosus* GG and *Lcb. casei* strain Shirata inhibited cell growth in the MGH and RT112 bladder cancer cell lines. Bladder cancer was induced in that study by inoculating MB49 cells in C57BL/6 mice, which were then administered *Lcb. rhamnosus* GG. The group fed *Lcb. rhamnosus* GG exhibited significantly reduced tumor formation and growth. The authors attributed this effect to immunomodulation, as indicated by increased spleen CD3, CD4, and CD8a T lymphocytes and natural killer (NK) cells [54]. An epidemiological study found that habitual intake of *Lcb. casei* strain Shirata reduced the risk of bladder cancer [63]. LAB are also effective at reducing the rate of recurrence. Furthermore, the 50% recurrence-free interval of bladder cancer was increased 1.8-fold by the oral administration of *Lcb. casei* in patients who had received transurethral resection of bladder tumors [2].

**Liver Cancer**

Cancer originating in the liver is uncommon in North America and Western Europe, whereas in Korea the liver is the third leading site of diagnosed cancers (after gastric and lung cancers) [4]. Hepatic metastases are most common from cancers of the gastrointestinal tract, lung, and breast, due to the large blood flow through the liver. Hepatic disease usually develops from hepatitis, which is caused by liver damage due to viruses, alcohol, and chemical compounds (e.g., aflatoxins, nitrosamines, andazo compounds) where the hepatitis leads to cirrhosis and finally to cancer. Therefore, liver cancer can be prevented by reducing liver damage [62].

There is considerable evidence that LAB reduce liver damage. Alteration of the gastrointestinal microflora to LAB and the antioxidant effects of LAB can reduce liver damage via the mechanisms described above [12]. Intragastric feeding of *Lcb. rhamnosus* (2 × 10^8 CFU/ml) reduced endotoxemia and alcohol-induced liver injury in the rat [61], and administration of *Lcb. acidophilus* reduced carbontetrachloride- and tert-butyl hydroperoxide-induced liver damage and β-glucuronidase activity. *Lcb. acidophilus* is more effective than a commercial hepatoprotective agent, dimethyl diphenyl bicarboxylate, at protecting against liver damage [25]. A mixture of *Lcb. rhamnosus* LC705 and *Propionibacterium freudenreichii* protected the liver from aflatoxin: the aflatoxin exposure was reduced by 55% in 45 healthy young men taking a dietary supplement containing LAB compared with another
### Table 1. Anticancer effects of LAB.

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Model</th>
<th>Strain</th>
<th>Effect</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Colon</td>
<td>HT-29</td>
<td><em>Bifidobacterium species</em></td>
<td>Reduce cell growth</td>
<td>[5]</td>
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<td></td>
<td></td>
<td></td>
<td>Increase differentiation</td>
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<tr>
<td></td>
<td>HT-29</td>
<td><em>Lactobacillus plantarum</em></td>
<td>Reduce DNA damage</td>
<td>[7]</td>
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<tr>
<td></td>
<td></td>
<td><em>Lactococcus lactis ssp. lactis</em></td>
<td>S-phase cell cycle arrest</td>
<td>[40]</td>
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<tr>
<td></td>
<td>SNUC2A</td>
<td><em>Bifidobacterium longum</em></td>
<td>Reduce aberrant crypts</td>
<td>[45, 75, 82]</td>
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<td>Reduce β-glucuronidase</td>
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<td>Reduce ammonia concentration</td>
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<td>Reduce Ras mutation</td>
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<td>Reduce ODC activity</td>
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<td></td>
<td>IQ-induced colorectal cancers in male F344 rats</td>
<td><em>Bifidobacterium longum</em></td>
<td>Reduce tumor incidence</td>
<td>[73]</td>
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<td></td>
<td>DMH-induced colorectal cancers in male F344 rats</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>Reduce tumor incidence</td>
<td>[16, 20]</td>
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<td></td>
<td>At least 2 colorectal tumors removed from 398 men and women</td>
<td><em>Lactobacillus casei</em></td>
<td>Reduce atypia</td>
<td>[29]</td>
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<tr>
<td></td>
<td>37 colon cancer patients and 43 polyectomized patients</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>Change fecal microflora</td>
<td>[72]</td>
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<tr>
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<td><em>Bifidobacterium lactis Bb12</em></td>
<td>Reduce proliferation</td>
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<td>Reduce fecal-water-induced DNA damage</td>
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<tr>
<td>Bladder</td>
<td>MGH3</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>Reduce cell growth</td>
<td>[80]</td>
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<tr>
<td></td>
<td>RT112</td>
<td><em>Lactobacillus casei strain Shirota</em></td>
<td>Increase in spleen CD3, CD4, and CD8a T lymphocytes and NK cells</td>
<td>[54]</td>
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<tr>
<td></td>
<td>MB49-injected C57BL/6 mice</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>Reduce bladder cancer</td>
<td>[63]</td>
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<td>Increase the 50% recurrence-free interval 1.8-fold</td>
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<td>Liver</td>
<td>180 bladder cancer patients</td>
<td><em>Lactobacillus casei strain Shirota</em></td>
<td>Reduce endotoxemia</td>
<td>[61]</td>
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<td>Patients with transurethral resection of the bladder tumor</td>
<td><em>Lactobacillus casei</em></td>
<td>Reduce liver injury</td>
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<td></td>
<td>Alcohol-fed male Wistar rats</td>
<td><em>Lactobacillus rhamnosus GG</em></td>
<td>Reduce liver damage</td>
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<td>Carbontetrachloride and tert-butyl hydroperoxide-fed ICR mice</td>
<td><em>Lactobacillus acidophilus</em></td>
<td>Reduce β-glucuronidase</td>
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<td></td>
<td>45 men</td>
<td><em>Lactobacillus rhamnosus LC705</em></td>
<td>Reduce aflatoxin exposure</td>
<td>[14]</td>
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<td></td>
<td></td>
<td></td>
<td>Reduce cell growth</td>
<td>[6]</td>
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<tr>
<td>Breast</td>
<td>MCF7</td>
<td><em>Bifidobacterium infantis</em></td>
<td>Reduce tumor growth</td>
<td>[13]</td>
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<td></td>
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<td><em>Bifidobacterium bifidum</em></td>
<td>Increase cytokines</td>
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<td></td>
<td><em>Bifidobacterium animalis</em></td>
<td>Reduce breast cancer</td>
<td>[88]</td>
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<td><em>Lactobacillus acidophilus</em></td>
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<td><em>Lactobacillus paracasei</em></td>
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<td></td>
<td>4T1-injected BALB/c mice</td>
<td><em>Lactobacillus helveticus R389</em></td>
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<tr>
<td>Stomach</td>
<td>133 breast cancer patients and 289 healthy controls</td>
<td>Fermented milk products</td>
<td>Reduce growth of <em>Helicobacter pylori</em></td>
<td>[74]</td>
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<td></td>
<td>Coculture of LAB and <em>Helicobacter pylori</em> in Brucella agar plates</td>
<td><em>Lactobacillus plantarum</em></td>
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<td>MLBPL1</td>
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<td><em>Helicobacter pylori</em>-infected C57BL/6 mice</td>
<td><em>Lactobacillus casei strain Shirota</em></td>
<td>Reduce colonization of <em>Helicobacter pylori</em></td>
<td>[81]</td>
</tr>
</tbody>
</table>

1 HT-29: human colon cancer cell line.  
2 SNUC2A: human colon adenocarcinoma cell line.  
3 ODC: ornithine decarboxylase.  
4 MGH: human bladder cancer cell line.  
5 RT112: human bladder cancer cell line.  
6 MB49: mouse bladder cancer cell line.  
7 MCF7: human breast cancer cell line.  
8 4T1: mouse mammary tumor cell line.
45 men taking a placebo [14]. Therefore, preventing liver damage by LAB may help to reduce the incidence of liver cancer. However, there have also been a few reports on a direct correlation between LAB and liver cancer, and hence this relationship needs to be studied further.

Breast Cancer

Breast cancer is the most-diagnosed female cancer in the United States [30]. In Korea, it is the second most common type of cancer after gastric cancer, and its incidence rate is steadily increasing, which may be due to the increasing popularity of the Western diet (as for colorectal cancer) [43]. Fermented milk containing five LAB (Bif. infantis, Bif. bifidum, Bif. animalis, Lcb. acidophilus, and Lcb. paracasei) inhibited the growth of the MCF7 breast cancer cell line [6]. De Moreno de LeBlanc et al. [13] employed an in vivo breast cancer model in which BALB/c mice received subcutaneous injections of 4T1 mouse mammary adenocarcinoma cells, and found that feeding the mice with fermented milk containing Lcb. helveticus R389 reduced tumor growth and increased cytokines such as interleukin (IL)-10 and IL-4. In a case-control study in The Netherlands, the consumption of fermented milk products was significant less among 133 breast cancer patients than among 289 healthy controls, suggesting that LAB can prevent breast cancer [88].

Gastric Cancer

The incidence of gastric cancer has declined in the United States since 1930, which may account for the decrease in Helicobacter (H) pylori infections due to antibiotic treatment [30]. However, in Korea, gastric cancer remains one of the most-diagnosed cancers, which is partly due to H. pylori infections not decreasing because of the presence of unique eating habits such as eating same dishes together [66]. Therefore, treatment of H. pylori is important to preventing gastric cancer in Korea. Most studies of gastric cancer related to LAB have involved their inhibitory effects against H. pylori [15]. However, we suggested other mechanism of how LAB can reduced gastric cancer in our study. The cytoplasmic fraction of L. lactis ssp. lactis induced apoptosis in the SNU-1 human adenocarcinoma cell line. We have also found that arginine deiminase is the active compound that induces apoptosis in this cell line [36, 41].

In summary, many studies have provided evidence that LAB can prevent different cancer types, such as colon, bladder, liver, breast, and gastric cancers (Table 1).

MECHANISMS OF ANTICANCER EFFECTS OF LAB

Alteration of the Gastrointestinal Microflora

Many genera and species of microorganisms inhabit the human gastrointestinal tract. Specific components of the gastrointestinal microflora provide health benefits, such as energy salvage, antagonism against pathogens, immune stimulation of the gut-associated lymphoid tissue, innate immunity against infections, and production of vitamins [23]. However, harmful bacteria such as C. perfringens can produce genotoxic, carcinogenic, and tumor-promoting components. The water in human feces exhibits genotoxicity and cytoxicity against colon cells. Furthermore, germ-free animals exhibit much lower incidences of colorectal cancer. These findings indicate that cancer may be at least partly due to the gastrointestinal microflora.

LAB enter the gut along with consumed food and are known to have beneficial effects on the resident bacteria of the gastrointestinal microflora [86]. They compete with other bacteria in the human body by producing inhibitory compounds (e.g., organic acids, hydrogen peroxide, bacteriocins, and reuterin) or competitively adhering to the epithelium. LAB can provide many health benefits if they can overcome harmful bacteria, and hence are called probiotics, which have been defined as "living microorganisms, which upon ingestion in certain numbers exert health benefits beyond inherent basic nutrition" [17].

The anticancer effects of LAB associated with alterations to the gastrointestinal microflora stem from mechanisms including antimutagenic effects and reducing harmful bacteria. Many mutagenic compounds are present in the Western meat-rich diet, and they can bind to the gastrointestinal tract, whereas LAB reduce the mutagenicity observed after exposure to the bacterial strains [46]. Ornager et al. [64] reported on the binding capacity of eight human gastrointestinal or LAB strains for mutagenic heterocyclic amines formed during the cooking of protein-rich food. The binding appears to be a physical phenomenon, mostly due to a cation-exchange mechanism, and it has been suggested that cell-wall peptidoglycans and polysaccharides are the two most important underlying elements [92]. It has also been shown that oral administration of Lcb. acidophilus inhibits the DNA damage induced by N-nitro-N-nitrosoguanidine, using the comet assay in both rat gastric and colonic mucosa [71].

Some microorganisms such as bacteroides, eubacteria, and clostridia produce metabolic end products that are considered to be carcinogenic and genotoxic compounds (e.g., nitrosoamines, heterocyclic amines, various aglycones, some azo compounds, and ammonia) [89]. In particular, β-glucuronidase, azoreductase, and nitroreductase are involved in producing these compounds. β-Glucuronidase has wide substrate specificity and can hydrolyze many different glucuronides to carcinogenic aglycones. Nitroreductase and azoreductase reduce nitro and azo compounds to aromatic amines, which are reactive intermediates whose end products are known mutagens and carcinogens. Since LAB exhibit low levels of these enzyme activities, increasing the LAB in gastrointestinal microflora will decrease the
activities of these enzymes. Oral supplementation of human and rat diets with viable Lcb. acidophilus decreases bacterial β-glucuronidase, nitroreductase, and azoreductase by about 50% [19, 21]. It has also been demonstrated that Lcb. acidophilus reduces β-glucuronidase in human-flora-associated rats. Moreover, feeding with Bif. longum also reduced β-glucuronidase activity by 30%.

H. pylori are Gram-negative, spiral-shaped, microaerophilic rods that colonize the human gastric mucosa by producing urease, which hydrolyzes urea to ammonium, leading to increased stomach pH that causes inflammatory diseases such as chronic gastritis. Gastric cancer is strongly related to a transition from normal mucosa to gastritis, which eventually leads to adenocarcinoma [68]. Therefore, an international agency for research on cancer has classified H. pylori as a class I carcinogen. LAB prevent or decrease the growth and colonization of H. pylori [22, 74]. An in vitro study found that Lcb. casei strain Shirota reduced H. pylori growth rates [81]. A significant reduction of H. pylori colonization in the Lactobacillus-treated group was also observed in the antrum and body mucosa in H. pylori-infected C57BL/6 mice, which was accompanied by a significant decrease in the associated chronic and active gastric mucosal inflammation. Other LAB such as Lcb. acidophilus 4356 have also been shown to attenuate the growth of H. pylori both in vivo and in vitro [3, 31, 42, 47, 59].

Enhancement of the Host’s Immune Response

Immunomodulation is a putative target for cancer therapy. Since Coley attempted to treat cancer patients by boosting the immune system with bacterial extracts, many researchers have attempted to cure cancer by immunomodulation [1]. Through advances in cellular and molecular immunology during the past two decades, many studies have shown that LAB enhance the host's immunoprotective system via mechanisms such as releasing cytokines and phagocytosis [90]. Intraperitoneal administration of Lcb. casei strain Shirota into tumor-bearing mice inhibited tumor growth and increased survival, because it induced the production of several cytokines such as interferon (IFN)-γ, IL-1, and tumor necrosis (TNF)-α [60]. Anti-TNF-α monoclonal antibody treatment completely abolished the antitumor effect of Lcb. casei strain Shirota in vivo. However, anti-IFN-γ and anti-IL-1β monoclonal antibodies had no effect [91]. Lcb. casei strain Shirota induced IL-12 and IFN-γ in murine splenocytes [33]. There are reports of other strains of LAB inducing cytokines and subsequently inhibiting tumors. Bif. longum and Bif. animalis induced inflammatory cytokines such as IL-6 and TNF-α [77]. Human bifidobacteria isolates induced H2O2, nitric oxide (NO), and IL-6 [67]. We previously found that Lcb. plantarum exerted the strongest effect on TNF-α, IL-6, and NO production out of six strains of major LAB found in kimchi (Leu. mesenteroides, Leu. citreum, Lcb. plantarum, Lcb. sake, Bif. longum, and Bif. lactis) in the RAW 264.7 murine macrophage cell line [27, 28]. We also observed that heat-killed Lec. lactis spp. lactis stimulated IFN-γ, IL-6, IL-12, and TNF-α in spleen cells. The cellular components of L. lactis spp. lactis induced only TNF-α in peritoneal-exudate cells. Intraperitoneal administration of whole-cell [37] and cytoplasmic fractions of L. lactis spp. lactis to male Balb/c mice resulted in the production of IFN-γ, IL-2, and IL-12 [38].

It has been shown that administering L. casei LC9018 to C57BL/6 mice enhanced the phagocytic activity of peritoneal macrophages [34]. Perdigon et al. [69] observed that macrophage and lymphocyte activities were enhanced in mice after administering a mixed culture of Lcb. acidophilus and Lcb. casei. This group also reported activation of peritoneal macrophages in mice after oral administration of Lcb. casei and Lcb. bulgaricus. Similar results were found for the oral delivery of S. thermophilus and Lcb. acidophilus [70] and the injection of heat-killed Lcb. casei to mice [76]. Lee et al. [50] recently demonstrated that administering the cytoplasmic fraction of Lcb. casei and Bif. longum as dietary supplements to Balb/c mice for 4 weeks enhanced the numbers of total T cells, NK cells, MHC class II+ cells, and CD4 CD8+ T cells. We have also demonstrated that oral administration of heat-killed L. lactis spp. lactis to male Balb/c mice induced phagocytic activity [38].

Antioxidative Activity

There are multiple lines of evidence from both laboratory and clinical studies that oxidative stresses imposed by reactive oxygen species (ROS) play a key role in all stages of carcinogenesis. Several antioxidants and free-radical generators are also known tumor promoters [8]. Many tumor promoters generate ROS, and the involvement of ROS (particularly H2O2) in the tumor promotion is supported by both in vivo and in vitro studies [24]. Therefore, dietary substances with antioxidant activities are anticipated to exert chemopreventive effects at all stages of carcinogenesis [52]. Kalzu et al. [32] found that Lcb. spp. SBT 208 exerted the strongest antioxidant effects out of 570 strains of LAB. Hemolysis of red blood cells was inhibited by administering the extract of Lcb. spp. SBT 208 to rats with vitamin E deficiency, suggesting that this LAB acts as a substitute for vitamin E. Lin and Yen [57] demonstrated that 19 strains of LAB exhibited antioxidant activities of 7–12% in intracellular cell-free extracts, which was due to their metal-ion-chelating and ROS-scavenging abilities. Lcb. acidophilus and Bif. longum inhibit lipid peroxidation, as demonstrated by two methods in which linoleic acid and the cell membrane of osteoblasts were used for lipid peroxidation. These strains protected against lipid oxidation by 33–46% in terms of linoleic acid peroxidation and by
22–37% in terms of cell membrane lipid peroxidation [58]. Both intact-cell and intracellular-cell-free extracts exerted antioxidant activities [56]. Heat-killed cells of *Lcb. acidophilus* 606 also exert antiproliferative activity [11], which is due to the soluble polysaccharide fraction; this fraction also exhibits potent antioxidant activity.

**Antiproliferative Activity**

Cancer usually is defined as “uncontrolled cell growth”. The maintenance of homeostasis in normal mammalian tissues may involve a critical balance between cell proliferation and cell death, with external or internal causes upsetting this balance, resulting in cancer [26]. Therefore, strategies for keeping cells under fine control have been used to prevent cancer, whereby cancer cells are killed or their proliferation is inhibited [78]. We have screened the cytotoxicity in whole-cell, cytoplasm, and peptidoglycan fractions of 10 LAB on 11 types of cancer cell lines using the *H*-thymidine incorporation assay [40]. The peptidoglycan and cytoplasm fractions as well as heat-killed whole-cell fraction of LAB exhibited significant antiproliferative activities against several cancer cell lines. In particular, the cytoplasm fractions exhibited marked direct antiproliferative activities against colon and gastric cancer cell lines, whereas the peptidoglycans inhibited the growth of colon and bladder cancer cell lines. In particular, the cytoplasm fraction of *Lcc. lactis* ssp. *lactis* mostly inhibited the proliferation of the SNUC2A human colon cancer cell line by downregulation of cyclin-dependent kinase 2 and overexpression of cyclin A [39].

Although the precise mechanisms of the anticancer effects of LAB remain unclear, several possible mechanisms include alteration of the gastrointestinal microflora, enhancement of the host’s immune response, and antioxidative and antiproliferative activities (Fig. 1).

**CONCLUDING REMARKS**

LAB have traditionally been used to enhance the preservation properties, flavors, and textures of foods. The works of Metchnikoff heralded an emphasis of the health benefits of LAB. Nowadays, the functional food market is in the limelight, with many advertisements focusing on the functionality of foods [9, 10, 48]. However, some of these foods are very expensive and the safety of others is unclear. LAB may be particularly safe active ingredients of functional foods owing to their long history of use. LAB are already widely consumed in fermented foods such as yogurt, cheese, and *kimchi*. In this review, we have described the results from studies related to the anticancer effects of LAB. However, most of these studies have only described the phenotype of the anticancer effects of LAB, and hence further investigations into the direct mechanisms and molecular targets are needed to clarify these effects. A better understanding about cancer and LAB may significantly contribute to improvements in the health of populations worldwide.

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