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Chapter 59

Probiotics in Cancer Prevention, Updating the Evidence

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1 INTRODUCTION

Probiotics are live microorganisms that, when taken orally, survive passage through the GI tract to apply a beneficial consequence. It has been suggested that probiotics have a significant role in the treatment and/or prevention of cancer. When probiotics are ingested in sufficient amounts, they supply health benefits to the host. "Probiotic" refers to viable microorganisms that promote or support a beneficial balance of the microbial population of the gastrointestinal tract (Holzapfel et al., 2001; Homayouni et al., 2008a,b). In addition to improving gut health (FAO/WHO, 2001; Homayouni, 2009), immunity (Galdeano et al., 2007), and protection against harmful microorganisms (Soccol et al., 2010), probiotics have been documented to exert other health-promoting effects by several mechanisms, such as anticarcinogenic properties (Bengmark et al., 1998; Mack et al., 1999; Homayouni et al., 2012a,b) and the prevention of cancer, especially colon and bladder (Sanders, 2006; Homayouni, 2008).

Cancer is defined as the abnormal division and reproduction of cells. Cancer cachexia is a syndrome of progressive nutritional depletion which causes significant morbidity and mortality in cancer patients (Figure 59.1). Annually in the United States, cancer is responsible for almost one out of every four deaths (ACS, 2009). It is estimated that 50-70% of cancer deaths are potentially preventable by decreasing high-risk behaviors and up to 80-90% of the patients, and between 20% and 25% of the cancer patients die directly as a result of the cachexia.

Complications caused by infections are the most important cause of morbidity and mortality in patients with cancer, and also the most complicated to treat. Often an early death results before remission can be achieved. Cancer patients are in an immune-compromised state due to the malignancy itself, drug-induced bone marrow suppression, treatment with chemotherapy or radiotherapy, and general condition deterioration. The main source of infection is endogenous intestinal microbiota. Infection is preceded by bowel colonization by pathogenic bacteria, followed by translocation through the gut mucosa and systemic distribution. There are numerous factors leading to interruption of the gut barrier function, such as intestinal microbial imbalance as a result of the use of antimicrobial agents, mucositis caused by anticancer agents, malnutrition, and general health worsening. Probiotics as live microorganisms have been used for prophylaxis and treatment for some infectious diseases. Their valuable effects include stimulation of gut immunity, competition for nutrition with pathogenic bacteria, bacteriocin production, organic acids production, competitive inhibition of bacterial attachment sites, and increased *trans*-epithelial resistance. The probiotic strains are capable of not only preventing infections but also some have effective antitumor effects in rodents and in humans. An effect of probiotics on the systemic immune improvement has been confirmed, especially on the proliferation and activation of natural killer cells in peripheral blood mononuclear cells, which play a critical role in immune surveillance against tumor growth and viral infections. The *Bifidobacterium breve* strain Yakult (BBG-01) is a probiotic strain that is generally known as safe after 30 years of use without a single report of adverse effects aggravated by this strain and has proven ability to alter intestinal microbiota by eradicating pathogenic bacteria such as *Campylobacter*, Candida, and Enterococcus after oral administration.

Diet plays an important role in the etiology of cancer. Nutritional support, in addressing the specific needs of this group of patients, is required to help improve prognosis and reduce the consequences of cancer-associated nutritional deficiency. Effective therapy improves patients' quality of life and also is survival. Early intervention with nutritional supplementation has been shown to halt malnutrition and may improve outcome in some patients. That increased nutritional intake
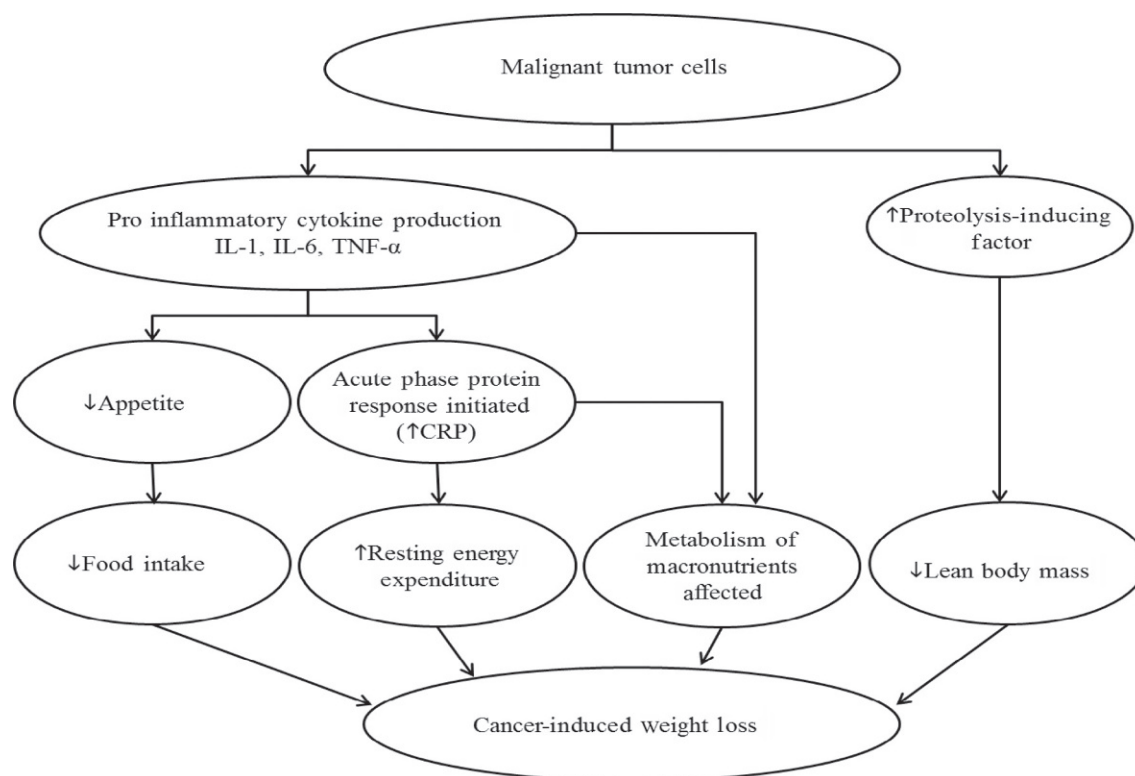
FIGURE 59.1   Metabolic pathogenesis of cancer cachexia.

is insufficient to prevent the development of cachexia, reflecting the complex pathogenesis of this condition. Some dietary factors, for instance probiotics, have a role in establishing a healthy bowel, including the risk for developing cancer. *Lactobacillus acidophilus*, *Lactobacillus casei* Shirota strain, and *Lactobacillus* GG have been shown to have inhibitory properties on chemically induced tumors in animals (De Roos and Katan, 2000; McFarland, 2000). Other studies indicate that specific strains of probiotic bacteria may be able to downregulate intestinal microbial enzyme activities (McFarland, 2000). Key physiological functions that might be related to cancer risk include control of epithelial cell proliferation and differentiation, production of essential nutrients and/or bioactive food components, prevention of overgrowth of pathogenic organisms, and stimulation of intestinal immunity (Tappenden and Deutsch, 2007).

There has been published no review paper about cancer and probiotic, focusing on the mechanisms of action, in the last decade. The aim of this chapter is to discuss the preventive and therapeutic effects of probiotics in cancer.

2 PROBIOTICS

The word "probiotic" is derived from the Greek word meaning "for life." Probiotics are defined as live organisms that, when ingested in adequate amounts, exert a health benefit to the host. "Probiotic" refers to viable microorganisms that promote or support a beneficial balance of the microbial population of the gastrointestinal tract (Holzapfel et al., 2001; Homayouni et al., 2008a,b). The human gastrointestinal microbiota is approximately 300-500 bacterial species comprising nearly 2 million genes (the "microbiome"). Indeed, the number of bacteria within the gut is about 10 times that of all of the cells in the human body (Guarner and Malagelada, 2003). A probiotic when ingested in adequate amounts exerts a health benefit to the host (FAO/WHO, 2001). The normal enteric bacterial flora influences a variety of intestinal functions and plays a key role in nutrition, in maintaining the integrity of the epithelial barrier, in the development of mucosal immunity, and in host metabolism (FAO/WHO, 2001). Probiotic food is an example of functional foods that has been the focus of intense research activity in recent years. The term probiotics usually refers to highly selected lactic acid bacteria with defined gut survival properties and associated biological activities, which can be ingested in fermented milk products or as a supplement (Salminen et al., 1998). A considerable amount of literature has been published on the application of probiotic bacterium in animal and human studies. In addition to improving gut health (FAO/WHO, 2001; Homayouni, 2009) and immunity (Galdeano et al., 2007), probiotics have been promoting the nonimmunologic defense barrier in the gut, including

normalization of increased intestinal permeability (Isolauri et al, 1993) and altered gut microecology (Isolauri et al., 1994) and improvement of the intestine's immunologic barrier, particularly intestinal IgA responses (Kaila et al., 1992), and alleviation of intestinal inflammatory response (Majarmaa and Isolauri, 1997), documented to exert other health promoting effects by several mechanisms. Some other health benefits of probiotics are controlling infection severity (Shu et al., 2000), hypertension (Yeo and Liong, 2010), and rotaviral-associated diarrhea (Duffy et al., 1993). Probiotics have antioxidative effects (Songisepp et al., 2004), anticarcinogenic properties (Bengmark et al., 1998; Mack et al., 1999), and they have the capacity to prevent cancer, especially colon and bladder (Sanders, 2006). It has been proved that probiotics can improve arthritis (Baharav et al., 2004), reduce dermatitis and allergic symptoms, especially in infants and pregnant women (Weston et al., 2005; Ouwehand, 2007), diminish tumor growth (Salgado et al., 2002), prevent gastrointestinal disorders (Homayouni and Ejtahed, 2009), such as ulcerative colitis (Pronio et al., 2008), and Crohn's disease (Garcia Vilela et al., 2008), prevent dental caries (Haukioja, 2010), improve performance (Sultan et al., 2006), and prevent osteoporosis (Lourens-Hattingh and Viljoen, 2001) and obesity (DiBaise et al., 2008).

3   CANCER

Cancer involves the abnormal division and reproduction of cells that can spread throughout the body. Usually thought of as a single disease, cancer actually consists of more than 100 distinct types (Grant, 2012).

3.1   Epidemiology

The American Cancer Society (ACS) predicts that the lifetime risk for developing cancer in the United States is slightly less than half of men and a little more than one-third of women (ACS, 2009). Annually in the United States, cancer is responsible for almost one out of every four deaths (ACS, 2009). Evidence suggests that one-third of the more than 560,000 cancer deaths may be attributed to nutrition and lifestyle behaviors such as poor diet, physical inactivity, alcohol use, overweight, and obesity. Almost an additional 171,000 cancer deaths are caused by tobacco use (ACS, 2010). It is estimated that 50-70% of cancer deaths are potentially preventable by decreasing high-risk behaviors; with approximately 30% of cancer deaths attributed to tobacco use and at least an additional 30% to poor nutrition (Brawer et al., 2009). The cost of cancer care in the United States has doubled in the past 20 years to more than $48 billion annually (NCI, 2010). Private insurance pays for 50% of the cost, Medicare coverage accounts for 34%, and Medicaid payment and other public programs cover the difference. Most medical-care spending for cancer has shifted away from an inpatient care setting to outpatient care and treatment.

3.2   Etiology

The most prevalent types of cancer diagnosed in the United States are prostate, lung and bronchus, colorectal, and urinary bladder cancers for men; and breast, lung and bronchus, colorectal, and uterine cancers for women. The ACS established 2015 Challenge Goals to improve cancer prevention and early detection efforts for lowering cancer incidence and mortality rates. These national recommendations outline specific measures to expand the use of established screening guidelines for the early detection of cancer, and ways to influence individual health behaviors such as protection from the sun, reducing tobacco use, maintaining a healthy body weight, improving diet, and increasing regular physical activity (ACS, 2010).

3.3   Risk Factors

Most environmental risk factors are theoretically controllable to some extent by avoiding high risk factors and supplementing protective factors as much as possible. Major avoidable risk factors include: tobacco, betel quid and chewing tobacco, diet, infection, occupation, alcohol, sunlight, radiation, pollution, medicine and medical procedures, industrial products, food additives, reproductive factors, sexual behavior, obesity, exercise (sedentary workers), and stress. Diet plays an important role in the etiology of cancer, but its relation to cancer is complicated. Excess intake of some food components such as fat, calorie, and salt and insufficient intake of some other food components such as dietary fiber, fresh vegetables, and fruits elevate risks of cancer of the esophagus, stomach, colon-rectum, breast, and some other sites. It is important to avoid excess intake of fat, calories, and salt. However, it is not easy to change dietary habits and food processing methods. Thus, diet will also remain a major risk factor of cancer in the twenty-first century. Some dietary factors can have a role in cancer prevention and/or treatment. For instance, probiotics, as viable microorganisms, have been suggested to have a critical role in setting the tone for a healthy bowel, including the risk for developing cancer.

3.4   Treatment

The common ways for treatment or control of cancer consist of medical and nutritional management. Medical techniques that are common in cancer therapy or control are surgery, radiation-therapy, chemotherapy, biotherapy, and hematopoietic cell transplantation. Eating behaviors play a very important role in health promotion and disease prevention. Chemoprevention involves specific compounds or drugs used to prevent, delay, or retard the development of cancer (Kashfi, 2009). One of the important dietary compounds that has a significant role in cancer treatment and/or control is probiotics, live microorganisms, that, when administered in adequate amounts, confer a health benefit on the host.

4   PROBIOTIC AND CANCER

A number of studies have focused on the effect of probiotics on intestinal microecology and cancer. *L. acidophilus*, *L. casei* Shirota strain, and *Lactobacillus* GG have been shown to have inhibitory properties on chemically induced tumors in animals (De Roos and Katan, 2000; McFarland, 2000). One study has illustrated that additional mechanisms produced by probiotic ingestion may play a role in protection from pathogens, such as diminishing adherence by inducing the secretion of specific mucins through induction of MUC genes in the gut (Mack et al., 2003), thus modulating the barrier effect of the gut. Other studies indicate that specific strains of probiotic bacteria may be able to downregulate intestinal microbial enzyme activities (McFarland, 2000). This phenomenon may then decrease carcinogen-activating microbial enzymes and has a beneficial effect in the colon, the urinary tract, and the bladder. However, further studies, especially human studies, are needed in this area. Reports on the benefits of oral administration of probiotic cultured milks and lactic acid bacteria on tumors have been connected with changes related to tumor induction and promotion (Gorbach et al., 2004). The colonic microbiota has been suggested to have a critical role in setting the tone for a healthy bowel including the risk for developing cancer (O'Keefe, 2008). Key physiological functions that might be related to cancer risk include control of epithelial cell proliferation and differentiation, production of essential nutrients and/or bioactive food components, prevention of overgrowth of pathogenic organisms, and stimulation of intestinal immunity (Tappenden and Deutsch, 2007). Bacteria can influence cancer risk by modifying metabolism of dietary components, which are more biologically active. For example, short-chain fatty acids, which are formed from the bacterial fermentation of indigestible carbohydrates, are nutrients and growth signals for the intestinal epithelium and may play a role in colon cancer prevention (Mai, 2004). Butyrate is the most widely studied of these short-chain fatty acids and the preferred energy source of colonocytes. In normal colonocytes, butyrate prevents apoptosis and subsequent mucosal atrophy (Wachtershauser and Stein, 2000; Klampfer et al., 2003). So, butyrate protects human colon cells from DNA damage (Ebert et al., 2003). In addition to butyrate, bacteria are involved in the formation of another group of beneficial fatty acids, namely, conjugated linoleic acids (CLAs). These are a group of isomers of linoleic acid possessing anti-inflammatory and cancer-preventive properties (Wong et al., 2005). Several studies have investigated the conversion of linoleic acid to CLA when incubated with various strains of lactobacilli and *bifidobacteria* (Sengupta et al., 2006; Ewaschuk et al., 2006). A combination of probiotic bacteria has been shown to convert linoleic acid to CLA, decreasing cancer cell viability and inducing apoptosis (Wong et al., 2005).

4.1   Probiotics and Anticancer Drug Metabolism

Drug metabolisms by intestinal microbiota contribute to the pharmacological profile of various drugs. Hydrolysis of drug and its conjugates by biliary system is not only responsible for enterohepatic circulation of a drug but also responsible for its distribution to a small area accumulation of a drug in the enterocytes. Bacterial hydrolases that may modulate drug pharmacokinetics include β-glucuronidase, β-glucosidase, amide hydrolase, and arylsulfotransferase. Probiotics may modulate anticancer drugs' pharmacokinetics by varying composition and metabolic activity of the microbiota. More research is necessary to examine the role of probiotics modulation of bacterial enzyme activity during chemotherapy.

4.2   Animal Studies

Oral administration of lactic acid bacteria has been shown to effectively reduce DNA damage, induced by chemical carcinogens, in gastric and colonic mucosa in rats. Pool-Zobel et al. (1996) reported, using the comet assay, that *L. acidophilus*, *Lactobacillus gasseri*, *Lactobacillus confusus*, *Streptococcus thermophilus*, *B. breve*, and *Bifidobacterium longum* were antigenotoxic toward *N*-nitro-Nnitrosoguanidine (MNNG). Certain strains of lactic acid bacteria have also been found to prevent putative preneoplastic lesions or tumors induced by carcinogens. Goldin et al. (1996) showed that a specific strain of *L. casei* subsp. *rhamnosus* designated GG can interfere with the initiation or early promotional stages of DMH-induced intestinal tumorigenesis and that this effect is most pronounced for animals fed a high-fat diet. Reddy and Rivenson (1993) reported that lyophilized cultures of *B. longum*

administered in the diet of rat inhibited liver, colon, and mammary tumors, induced by the food mutagen IQ. In another study, Kohwi et al. (1978) demonstrated the potential of two *Bifidobacterium* species, *Bifidobacterium infantis*, and *Bifidobacterium adolescentis*, injected either subcutaneously or intraperitoneally in to BALB/c mice to inhibit 3-methylcholanthrene-induced tumors. There is additional direct evidence for antitumor activities of lactic acid bacteria obtained in studies using preimplanted tumor cells in animal models. It has been demonstrated that feeding of fermented milk or cultures containing lactic acid bacteria inhibited the growth of tumor cells injected into mice (Friend et al., 1982; Kato et al., 1981).

4.3   Human Studies

Consumption of lactobacilli by volunteers has been shown to reduce the mutagenicity of urine and feces associated with the ingestion of carcinogens in cooked meat (Lidbeck et al., 1992a,b). Hayatsu and Hayatsu (1993) also demonstrated a marked suppressing effect of orally administered *L. casei* on the urinary mutagenicity arising from ingestion of fried ground beef in the human. It is possible that the *L. acidophilus* supplements are influencing excretion of mutagens by simply binding them in the intestine. Mucosal cell proliferative activity in upper colonic crypts of patients with colon adenomas significantly decreased after the administration of *L. acidophilus* and *Bifidobacterium bifidus* cultures (Biasco et al., 1991).

   An epidemiological study performed in Finland demonstrated that, despite a high-fat intake, the colon cancer incidence was lower than in other countries because of the high consumption of milk, yogurt, and other dairy products (Malhotra, 1977). In conclusion, data from human intervention studies are of paramount importance in providing evidence that probiotics, prebiotics, and fermented milk consumption are causally related to reduction in cancer risk. This, therefore, indicates an area of high priority for future studies.

   Between the possible mechanisms of probiotic therapy is the upgrade of the endogeneous defense barrier of the gut. Promotion of nonimmunologic protection barrier in the gut includes regulation of increased intestinal permeability (Isolauri et al., 1993) and improved gut microecology (Isolauri et al., 1994). Another description for the gut alleviating effect could be improvement of the intestine's immunologic barrier (Kaila et al., 1992), and lessening of intestinal inflammatory response (Majarmaa and Isolauri 1997). These data point to the conclusion that probiotics can be used as inventive tools for treating dysfunctions of the gut mucosal barrier (Salminen et al., 1998). Many of the probiotic effects are mediated via immune regulation, in certain by control of the balance of proinflammatory and anti-inflammatory cytokines. The results of the studies indicate that probiotic bacteria have several immunomodulatory effects, adjuvant-like properties, and anti-inflammatory properties. Moreover, both quantitative and qualitative differences in immune prohibiting, immune elimination, and immune regulation exist among candidate probiotic bacteria. These observations reviewed together suggest that specific immunomodulatory properties of probiotic bacteria should be considered during the development of clinical uses for comprehensive target populations.

5   APPROPRIATE PROBIOTIC STRAINS FOR USE IN CANCER THERAPY

Lactic acid bacteria and *Bifidobacteria* are the most common types of microbes used as probiotics, while certain yeasts and bacilli may also be beneficial to the host. The immunomodulatory effect of probiotic bacteria was postulated by Metchnikoff over 100 years ago (Anukam and Reid, 2007). There has been an increased interest in the scientific community on the protective roles of probiotics on intestinal diseases, especially colon carcinogenesis. Orlando et al. (2009) found that *Lactobacillus* GG administration induced a significant reduction in polyamine biosynthesis in both the HGC-27 and DLD-1 cancer cell lines. Kim et al. (2008a,b) assessed the anticancer activity and bacterial enzyme inhibition of *B. adolescentis* SPM0212. The strain inhibited the proliferation of three human colon cancer cell lines: HT-29, SW 480, and $CaCo_2$ and also dose-dependently inhibited TNF-α production and changes in cellular morphology. Urbanska et al. (2009) studied the properties of microencapsulated probiotic bacterial cells in a yogurt formulation in MIN mice carrying a germline APC mutation. Daily oral administration of the microencapsulated *L. acidophilus* resulted insignificant suppression of colon tumor incidence, tumor-multiplicity, and reduced tumor size. Certain strains of lactic acid bacteria have been found to prevent putative preneoplastic lesions or tumors induced by carcinogens. Goldin et al. (1996) showed that a specific strain of *L. casei* subsp. *rhamnosus* designated GG can interfere with the initiation or early promotional stages of DMH-induced intestinal tumorigenesis. Consumption of large quantities of dairy products such as yogurt and fermented milk containing *Lactobacillus* or *Bifidobacterium* may be related to a lower incidence of colon cancer (Shahani and Ayebo, 1980). Consumption of lactobacilli by volunteers has been shown to reduce the mutagenicity of urine and feces associated with the ingestion of carcinogens in cooked meat (Lidbeck et al., 1992a,b). It is possible that the *L. acidophilus* supplements are influencing excretion of mutagens by simply binding them in the intestine. However, lactic acid bacteria have also been shown to affect the host. Mucosal cell proliferative activity in upper colonic crypts of patients with colon adenomas significantly decreased after the administration of *L. acidophilus* and *B. bifidus* cultures (Biasco et al., 1991).

Probiotics are shown to improve proliferation of immune cells (De Simone et al., 1993) and prompt production of pro-inflammatory cytokines, such as tumor necrosis factor and interleukin 6 (Miettinen et al., 1996). In comparison, probiotic bacteria intermediate suppression of lymphocyte propagation and cytokine production by T cells (Sütas et al., 1996). One study group tried to compare the antiproliferative outcome of several probiotic bacterial strains in their nonviable systems (Pessi et al., 1999). The probiotic strains were cultivated. When the rate of proliferation was compared among cultures containing an indistinguishable protein concentration, a hierarchy of immunomodulation between probiotics was shown. They showed that particular probiotic bacteria possess significant anti-inflammatory properties similar to a therapeutic pharmaceutical agent.

6   EFFECTIVE DOSAGE OF PROBIOTICS FOR CANCER THERAPY

Little is known about the optimal amount of live probiotic bacteria to be administered (Aureli et al., 2011); this quantity is not easy to determine: it is strain-specific, and it probably depends on the type of benefit sought for with the administration of probiotics (different functional effects may require different amounts of live probiotics). Of course, the overall amount cannot be low, if the aim is to markedly influence the composition of the microbiota of the host. It should be emphasized that, in cases of microbial associations, each species in "competition" with a functional action must be provided in appropriate amounts. In the absence of specific dose-response studies, however, some points reported in the AFSSA paper (AFFSA, 2005) are worth reiterating: (1) "The dose of probiotics ingested is an important factor to obtain high concentrations in the various compartments of the gastrointestinal tract." (2) "It is often said that probiotic concentrations must be greater than or equal to 10^6 CFU/mL in the small intestine (ileum) and 10^8 CFU/g in the colon, but the scientific basis for these statements is relatively weak." (3) "The concentrations in the colon have been proposed because they correspond to less than 1/1000 of the autochthonous microbiota present (which it could be reasonably expected has more chance of being active than microbiota present at even lower levels)." Sivieri et al. (2008) conducted a placebo-controlled design trial involving 30 male Wistar SPF rats to evaluate the effects of a probiotic strain, *Enterococcus faecium* CRL 183 on the incidence of colorectal tumors induced by 1,2-dimethlhydrazine (DMH). The authors reported that rats administered with *E. faecium* CRL 183(10^8 CFU/ml) for 24 weeks showed a 40% reduction of adenocarcinoma incidence and diminished mean tumor volumes compared to rats without the administration of probiotics. Singh et al. (1997) conducted a placebo-controlled design trial to evaluate the effects of *B. longum* on 60 male F344 azoxymethane (AOM)-induced colon carcinogenesis rats. The rats were fed a modified AIN-76A diet containing 0% or 2% lyophilized cultures of *B. longum* (4×10^{10} live cells/g diet) and administered AOM dissolved in normal saline, once weekly for 2 weeks and killed on 40 weeks after second AOM injection to evaluate the incidences of colon tumor. The authors revealed that the administration of *B. longum* significantly reduced the incidence of colon adenocarcinomas, colon tumor multiplicity in terms of tumors/animal, and tumors/tumor-bearing animal compared to those on the control diet. Lidbeck et al. (1991) studied the effect of *L. acidophilus*-fermented milk on fecal microbiota and β-glucuronidase activity in 14 colon cancerpatients. The authors reported that the feeding of *L. acidophilus* (10^{11} CFU/day) for 6 weeks caused a reduction of *Escherichia coli* and increased the number of lactobacilli in the feces that subsequently led to a 14% reduction of β-glucuronidase activity, an enzyme which generates carcinogens in the digestive system of humans. It was supported by Ling et al. (1994) that studied the effect of *Lactobacillus* strain GG on the fecal enzyme activity in 64 subjects. The authors found that the consumption of yogurt containing viable *Lactobacillus* strain GG (10^{11} CFU/L) decreased not only fecal β-glucuronidase but also other fecal enzyme activities such as nitroreductase and glycocholic acid hydrolase activities ($P < 0.05$) after consumption of yogurt containing probiotic for 4 weeks. Same observation was reported by Marteau et al. (1990) that the nitro-reductase activity was significantly reduced ($P < 0.05$) in nine healthy volunteers after administration of 100 g/day of fermented milk product containing *L. acidophilus* (10^7 CFU/g), *Bifidobacterium bifidum* (10^8 CFU/g), *Streptoccoccus* (*Lactococcus*) *lactis* (10^8 CFU/g), and *Streptoccoccus cremoris* (*Lactococcuslactis* subsp. *cremoris*) *lactis* (10^8 CFU/g) for 3 weeks. The authors also found that the β-glucosidase activity was significantly increased ($P < 0.05$) after the consumption of probiotic fermented milk. In another study, Goldin and Gorbach (1984) evaluated the effects of milk containing *L. acidophilus* on fecal enzyme activity in 16 women and 5 men. The authors found that the oral administration of *L. acidophilus* (2×10^6 CFU/ml) for 4 weeks significantly reduced ($P < 0.05$) most of the fecal enzyme activities such as β-glucuronidase, nitroreductase, and azoreductase with two to four fold reductions during the period of lactobacilli feeding.

7   DURATION OF PROBIOTIC THERAPY IN PATIENTS WITH CANCER

According to the findings of several studies, the average duration for receiving the probiotic effect in cancer prevention and/or treatment may be 4-6 weeks. Sivieri et al. (2008) reported that rats administered with *E. faecium* CRL 183 for 24 weeks

showed a 40% reduction of adenocarcinoma. Singh et al. (1997) revealed that the administration of *B. longum* once weekly for 2 weeks significantly reduced the incidence of colon adenocarcinomas, colon tumor multiplicity in terms of tumors/animal and tumors/tumor-bearing animal compared to those on the control diet. Lidbeck et al. (1991) reported that the feeding of *L. acidophilus* for 6 weeks caused a reduction of *E. coli* and increased the number of lactobacilli in the feces that subsequently led to a 14% reduction of β-glucuronidase activity. Ling et al. (1994) reported that the consumption of yogurt containing viable *Lactobacillus* strain GG decreased not only fecal β-glucuronidase but also other fecal enzyme activities such as nitroreductase and glycocholic acid hydrolase activities ($P < 0.05$) after consumption of yogurt containing probiotic for 4 weeks. Marteau et al. (1990) found that the β-glucosidase activity was significantly increased ($P < 0.05$) after the consumption of probiotic fermented milk for 3 weeks. Goldin and Gorbach (1984) evaluated that the oral administration of *L. acidophilus* (2×10^6 CFU/ml) for 4 weeks significantly reduced ($P < 0.05$) most of the fecal enzyme activities during the period of lactobacilli feeding. Matsumoto and Benno (2004) reported that the consumption of 100 g/day of *B. lactis*-containing yogurt for 2 weeks significantly reduced the faces mutagenicity of seven healthy subjects (Table 59.1).

TABLE 59.1 Effective Dose and Duration of Probiotics in Cancer Treatment and/or Prevention

| Probiotic strain	Animals/ subjects	Dose and duration of the study	Effects	References
In animal studies				
B. longum	Male F344 rats	2×10^{10} CFU/g 5 weeks	Inhibition in ACF formation of about 50%	Kulkarni and Reddy (1994)
*B. longum*on	Rats	4×10^{10} live cells/g diet 2 weeks	Significant reduction in the incidence of colon adenocarcinomas	Singh et al. (1997)
B. longum	Rats	6×10^9 CFU/day	A significant reduction of 26% in total ACF by comparison to control animals	Rowland et al. (1998)
B. polyfermenticus	Rats	3×10^8 cfu/1.3 g	50% reduction in ACF formation	Park et al. (2007)
Enterococcus faecium CRL 183	Wistar SPF rats	10^8 CFU/ml 24 weeks	40% reduction of adenocarcinoma incidence	Sivieri et al. (2008)
B. adolescentis SPM0212	Rats	1×10^8 CFU per day 3 weeks	The strain inhibited the proliferation of three colon cancer cell lines	Kim et al. (2008a,b)
L. acidophilus bacterial	Mice	10^{10} cfu/mL	Insignificant suppression of colon tumor incidence	Urbanska et al. (2009)
In human studies				
L. acidophilus	16 women and 5 men	2×10^6 CFU/ml 4 weeks	Significant reduction ($P < 0.05$) in most of the fecal enzyme activities	Goldin and Gorbach (1984)
L. acidophilus	Human subjects	2×10^6 CFU/ml 4 weeks	β-Glucuronidase activity decreased slightly after four weeks of lactobacillus feeding	Ayebo et al. (1980)
L. acidophilus	14 colon cancer patients	10^{11} CFU/day 6 weeks	14% reduction of β-glucuronidase activity	Lidbeck et al. (1991)
L. acidophilus	11 subjects	$1\text{-}5 \times 10^{11}$ cells per day 1 week	Decreased urinary excretion of mutagens by 50-70%	Lidbeck et al. (1992a,b)
L. casei	4 males and 2 females	10^{10} cells/g 3 weeks	Suppressing effect on the urinary mutagenicity	Hayatsu and Hayatsu (1993)
Lactobacillus GG	64 subjects	10^{11} CFU/L 4 weeks	Decreased fecal β-glucuronidase	Ling et al. (1994)
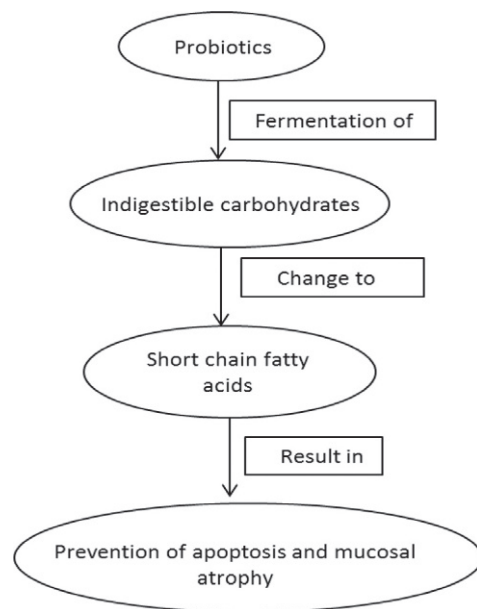
FIGURE 59.2   One of the mechanisms in cancer prevention by probiotics.

8   MECHANISMS BY WHICH PROBIOTIC BACTERIA MAY INHIBIT CANCER

The precise mechanisms by which probiotics may inhibit cancer are currently unknown. Such mechanisms might, however, include: an alteration of the metabolic activities of intestinal microbiota; an alteration of physicochemical conditions in the colon; the binding and degradation of potential carcinogens; quantitative and/or qualitative alterations in the intestinal microbiota incriminated in producing putative carcinogen(s) and promoters (e.g., bile acid-metabolizing bacteria); the production of antitumorigenic or antimutagenic compounds (Figure 59.2); an enhancement of the host's immune-response; and effects on host physiology (Rafter, 2003). The mechanisms in which probiotics act may be categorized as:

1. Improving resistance to colonization by pathogens by lactic microflora production (Gibson and MacFarlane, 1994).
2. Modulate anticancer drug's phrmacokinetics by altering composition and metabolic activity of the micrflora (Xue et al., 2011).
3. Enhancing production of short-chain fatty acid by main energy source for enterocytes to prevent from inflammation (Wilson et al., 1996).
4. Modulating the immune system by mucin production (Bakker-Zierikzee et al., 2006; Hosono et al., 2003).

9   CONCLUSION

This review confirms the potential efficacy of probiotics in cancer prevention and/or control by several mechanisms for instance stimulating the immune system, decreasing the incidence of infections, regulating gut inflammation, and binding toxic compounds. According to several human and animal studies, many of the specific probiotic bacteria and their metabolites have beneficial effects in cancer control and/or prevention. Consumption of *Lactobacillus* or *Bifidobacterium* in dosage of 10^{10}-10^{11} cfu/day for at least 4-6 weeks may lower incidence of cancer; however, more studies are needed to investigate the relationships between probiotics, diet, and cancer risk.

ACKNOWLEDGMENTS

REFERENCES

American Cancer Society, 2009. Cancer Facts & Figures. American Cancer Society, Atlanta.

American Cancer Society, 2010. Cancer Glossary.

Agence Francaise de Sécurité Sanitaire des Aliments/French Food Safety Agency (AFSSA), 2005. Effects of Probiotics and Prebiotics on Flora and Immunity in Adults.

Anukam, K.C., Reid, G., 2007. Probiotics: 100 years (1907–2007) after Elie Metchnikoff's observations. In: Mendez-Vilas, A. (Ed.), Communicating Current Research and Educational Topics and Trends in Applied Microbiology. Formatex.org, Spain, pp. 466–474.

Aureli, P., Capurso, L., Castellazzi, A.M., Clerici, M., Giovannini, M., Morelli, L., Poli, A., Pregliasco, F., Salvini, F., Zuccotti, G.V., 2011. Probiotics and health: an evidence-based review. Pharmacol. Res. 63, 366–376.

Ayebo, A.D., Angelo, I.A., Shahani, K.M., 1980. Effect of ingesting Lactobacillus acidophilus milk upon faecal flora and enzyme activity in humans. Milchwissenschaft 35, 730–733.

Baharav, E., Mor, F., Halpern, M., Weinberger, A., 2004. Lactobacillus GG bacteria ameliorate arthritis in Lewis rats. J. Nutr. 134, 1964–1969.

Bakker-Zierikzee, A.M., Van Tol, E.A.F., Kroes, H., Alles, M.S., Kok, F.J., Bindels, J.G., 2006. Faecal SIgA secretion in infants fed on pre- or probiotic infant formula. Pediatr. Allergy Immunol. 17, 134–140.

Bengmark, S., Aherne, S., Molin, G., Jeppsson, B., 1998. Intestina; colonising lactobacilii. J. Nutr. 14, 585–594.

Biasco, G., Paganelli, G.M., Brandi, G., Brillanti, S., Lami, F., Callegari, C., Gizzi, G., 1991. Effect of Lactobacillus acidophilus and Bifidobacterium bifidum on rectal cell kinetics and fecal pH. Ital. J. Gastroenterol. 23, 142.

Brawer, R., Brisbon, N., Plumb, J., 2009. Obesity and cancer. Prim. Care 36, 509–531.

De Roos, N., Katan, M., 2000. Effects of probiotic bacteria on diarrhea, lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. Am. J. Clin. Nutr. 71, 405–411.

De Simone, C., Vesely, R., Bianchi Salvadori, B., Jirillo, E., 1993. The role of probiotics in modulation of the immune system in man and in animals. Int. J. Immunother. 9, 23–28.

DiBaise, J.K., Zhang, H., Crowell, M.D., Krajmalnik-Brown, R., Decker, G.A., Rittmann, B.E., 2008. Gut microbiota and its possible relationship with obesity. Mayo Clin. Proc. 83, 460–469.

Duffy, L.C., Zielezny, M.A., Riepenhoff-Talty, M., Dryja, D., Sayahtaheri-Altaie, S., Griffiths, E., Ruffin, D., Barrett, H., Rossman, J., Ogra, P.L., 1993. Effectiveness of Bifidobacterium bifidum in experimentally induced MRV infection: dietary implications in formulas for newborns. Endocr. Regul. 27 (4), 223–229.

Ebert, M.N., Klinder, A., Peters, W.H., Schaferhenrich, A., Sendt, W., Scheele, J., et al., 2003. Expression of glutathione S-transferases (GSTs) in human colon cells and inducibility of GSTMs by butyrate. Carcinogenesis 10, 1637–1644.

Ewaschuk, J.B., Walker, J.W., Diaz, H., Madsen, K.L., 2006. Bioproduction of conjugated linoleic acid by probiotic bacteria occurs in vitro and in vivo in mice. J. Nutr. 136, 1483–1487.

FAO/WHO, 2001. FAO/WHO 'Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria'. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria, October.

Friend, B.A., Farmer, R.E., Shahani, K.M., 1982. Effect of feeding and intraperitoneal implantation of yogurt culture cells on Ehrlich ascites tumor. Milchwissenschaft 37, 708–710.

Galdeano, C.M., Leblanc, A.M., Vinderola, G., Bonet, M.E., Perdigon, G., 2007. Proposed model: mechanisms of immunomodulation induced by probiotic bacteria. Clin. Vaccine Immunol. 14, 485–492.

Garcia Vilela, E., De Lourdes De Abreu Ferrari, M., Oswaldo Da Gama Torres, H., Guerra Pinto, A., Carolina Carneiro Aguirre, A., Paiva Martins, F., Marcos Andrade Goulart, E., Sales Da Cunha, A., 2008. Influence of *Saccharomyces boulardii* on the intestinal permeability of patients with Crohn's disease in remission. Scand. J. Gastroenterol. 43 (7), 842–848.

Gibson, G.R., MacFarlane, G.T., 1994. Intestinal bacteria and disease. In: Gibson, S.A.W. (Ed.), Human Health: The Contribution of Microorganisms. Springer-Verlag, London, pp. 53–62.

Goldin, B.R., Gorbach, S.I., 1984. The effect of milk and Lactobacillus feeding on human intestinal bacterial enzyme activity. Am. J. Clin. Nutr. 39, 756–761.

Goldin, B.R., Gualtieri, L.J., Moore, R.P., 1996. The effect of Lactobacillus GG on the initiation and promotion of DMH induced intestinal tumors in the rat. Nutr. Cancer 25, 197–204.

Grant, B.L., 2012. Nutrition in Cancer Treatment: Continuum of Care, third ed. Nutrition Dimension/Gannett Education.

Guarner, F., Malagelada, J.R., 2003. Gut flora in health and disease. Lancet 361, 512–519.

Haukioja, A., 2010. Probiotics and oral health. Eur. J. Dent. 4, 348–355.

Hayatsu, H., Hayatsu, T., 1993. Suppressing effect of Lactobacillus caseia dministration on the urinary mutagenicity arising from ingestion of fried ground beef in the human. Cancer Lett. 73, 173–179.

Holzapfel, W.H., Habere, P., Geisen, R., Björkroth, J., Schillinger, U., 2001. Taxonomy and important features of probiotic microorganisms in food and nutrition. Am. J. Clin. Nutr. 73 (2), 365–373.

Homayouni, A., 2008. Therapeutical Effects of Functional Probiotic, Prebiotic and Synbiotic Foods. Tabriz University of Medical Sciences, Tabriz, pp. 30–32.

Homayouni, A., 2009. Letter to the editor. Food Chem. 114, 1073.

Homayouni, A., Ejtahed, H.S., 2009. The effect of probiotics in prevention and treatment of gastrointestinal disorders: a review. J. Microbiol. Biotechnol. 2, 53–60.

Homayouni, A., Azizi, A., Ehsani, M.R., Yarmand, M.S., Razavi, S.H., 2008a. Effect of microencapsulation and resistant starch on the probiotic survival and sensory properties of synbiotic ice cream. Food Chem. 111, 50–55.

Homayouni, A., Ehsani, M.R., Azizi, A., Razavi, S.H., Yarmand, M.S., 2008b. Spectrophotometrically evaluation of probiotic growth in liquid media. Asian J. Chem. 20, 2414–2420.

Homayouni, A., Payahoo, L., Azizi, A., 2012a. Effects of probiotics on lipid profile: a review. Am. J. Food Technol. 7, 251–265.

Homayouni, A., Azizi, A., Javadi, M., Mahdipour, S., Ejtahed, H., 2012b. Factors influencing probiotic survival in ice cream: a review. Int. J. Dairy Sci. 7, 1–10.

Hosono, A., Ozawa, A., Kato, R., Ohnishi, Y., Nakanishi, Y., Kimura, T., Nakamura, R., 2003. Dietary fructooligosaccharides induce immunoregulation of intestinal IgA secretion by murine Peyer's patch cells. Biosci. Biotechnol. Biochem. 67, 758–764.

Isolauri, E., Kaila, M., Arvola, T., et al., 1993. Diet during rotavirus enteritis affects jejunal permeability to macromolecules in suckling rats. Pediatr. Res. 33, 548–553.

Isolauri, E., Kaila, M., Mykkänen, H., Ling, W.H., Salminen, S., 1994. Oral bacteriotherapy for viral gastroenteritis. Dig. Dis. Sci. 39, 2595–2600.

Kaila, M., Isolauri, E., Soppi, E., Virtanen, E., Laine, S., Arvilommi, H., 1992. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human lactobacillus strain. Pediatr. Res. 32, 141–144.

Kashfi, K., 2009. Anti-inflammatory agents as cancer therapeutics. Adv. Pharmacol. 57, 31–89.

Kato, I., Kobayashi, S., Yokokura, T., Mutai, M., 1981. Antitumor activity of Lactobacillus casei in mice. Gann 72, 517–523.

Kim, Y., Lee, D., Kim, D., Cho, J., Yang, J., Chung, M., Kim, K., Ha, N., 2008a. Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by Bifidobacterium adolescentis SPM0212. Arch. Pharm. Res. 31, 467–468, PubMed: 18449504.

Kim, Y., Lee, D., Kim, D., Cho, J., Yang, J., Chung, M., Kim, K., Ha, N., 2008b. Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by Bifidobacterium adolescentis SPM0212. Arch. Pharm. Res. 468–473.

Klampfer, L., Huang, J., Sasazuki, T., Shirasawa, S., Augenlicht, L., 2003. Inhibition of interferon gamma signaling by the short chain fatty acid butyrate. Mol. Cancer Res. 1, 855–862.

Kohwi, T., Imai, K., Tamura, A., Hashimoto, Y., 1978. Antitumor effect of Bifidobacterium infantis in mice. Gann 69, 613–618.

Kulkarni, N., Reddy, B.S., 1994. Inhibitory effect of Bifidobacterium longum cultures on the azoxymethane induced aberrant crypt foci formation and faecal bacterial β-glucuronidase. Proc. Soc. Exp. Biol. Med. 207, 278–283.

Lidbeck, A., Geltner Allinger, U., Orrhage, K.M., Ottova, L., Brismar, B., Gustafsson, J.A., Rafter, J.J., Nord, C.E., 1991. Impact of Lactobacillus acidophilus supplements on the faecal microflora and soluble faecal bile acids in colon cancer patients. Microb. Ecol. Health Dis. 4, 81–88.

Lidbeck, A., Overvik, E., Rafter, J., Nord, C.E., Gustafsson, J.A., 1992a. Effect of Lactobacillus acidophilus supplements on mutagen excretion in feces and urine in humans. Microb. Ecol. Health Dis. 5, 59–67.

Lidbeck, A., Nord, C.E., Gustafsson, J.A., Rafter, J., 1992b. Lactobacilli, anticarcinogenic activities and human intestinal microflora. Eur. J. Cancer Prev. 1, 341–353.

Ling, W.H., Korpela, R., Mykkanen, H., Salminen, S., Hanninen, O., 1994. Lactobacillus strain GG supplementation decreases colonic hydrolytic and reductive enzyme activities in healthy female adults. J. Nutr. 124, 18–23.

Lourens-Hattingh, A., Viljoen, B.C., 2001. Yogurt as probiotic carrier food. Int. Dairy J. 11, 1–17.

Mack, D.R., Michail, S., Wei, S., McDougall, L., Hollingsworth, M.A., 1999. Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. Am. J. Physiol. Gastrointest. Liver Physiol. 276, 941–950.

Mack, D.R., Ahrne, S., Hyde, L., Wei, S., Hollingsworth, M.A., 2003. Extracellular MUC3 mucin secretion follows adherence of Lactobacillus strains to intestinal epithelial cells in vitro. Gut 52, 827–833.

Mai, V., 2004. Dietary modification of the intestinal microbiota. Nutr. Rev. 62, 235–242.

Majarmaa, H., Isolauri, E., 1997. Probiotics: a novel approach in the management of food allergy. J. Allergy Clin. Immunol. 99, 179–186.

Malhotra, S.L., 1977. Dietary factors in a study of colon cancer from cancer registry, with special reference to the role of saliva, milk, and fermented milk products and vegetable fibre. Med. Hypotheses 3, 122–134.

Marteau, P., Pochart, P., Flourie, B., Pellier, P., Santos, L., Desjeux, J.-H., Rambaud, J.-C., 1990. Effect of chronic ingestion of a fermented dairy product containing Lactobacillus acidophilus and Bifidobacterium bifidum on metabolic activities of the colonic flora in humans. Am. J. Clin. Nutr. 52, 685–688.

Matsumoto, M., Benno, Y., 2004. Consumption of Bifidobacterium lactis LKM512 yogurt reduces gut mutagenicity by increasing gut polyamine contents in healthy adult subjects. Mutat. Res. Fundam. Mol. Mech. Mutagen. 568, 147–153.

McFarland, L., 2000. A review of the evidence of health claims for biotherapeutic agents. Microb. Ecol. Health Dis. 12, 65–76.

Miettinen, M., Vuopio-Varkila, J., Varkila, K., 1996. Production of human tumor necrosis factor alpha, interleukin-6, and interleukin-10 is induced by lactic acid bacteria. Infect. Immun. 64, 5403–5405.

National Cancer Institute (NCI), 2010. Cancer Bulletin—Cost of Cancer Care Has Doubled in the Past 20 Years.

O'Keefe, S.J., 2008. Nutrition and colonic health: the critical role of the microbiota. Curr. Opin. Gastroenterol. 24, 51–58.

Orlando, A., Messa, C., Linsalata, M., Cavallini, A., Russo, F., 2009. Effects of Lactobacillus rhamnosus GG on proliferation and polyamine metabolism in HGC-27 human gastric and DLD-1 colonic cancer cell lines. Immunopharmacol. Immunotoxicol. 31, 108–116, PubMed: 19234959.

Ouwehand, A.C., 2007. Antiallergic effects of probiotics. J. Nutr. 137, 794–797.

Park, E., Jeon, G.I., Park, J.S., Paik, H.D., 2007. A probiotic strain of Bacillus polyfermenticus reduces DMH-induced precancerous lesions in F344 male rat. Biol. Pharm. Bull. 30, 569–574.

Pessi, T., Sütas, Y., Saxelin, M., Kallioinen, H., Isolauri, E., 1999. Antiproliferative effects of homogenates derived from five strains of candidate probiotic bacteria. Appl. Environ. Microbiol. 65, 475–478.

Pool-Zobel, B.L., Neudecker, C., Domizlaff, I., Ji, S., Schillinger, U., Rumney, C., Moretti, M., Vilarini, I., Scassellati-Sforzolini, R., Rowland, I., 1996. Lactobacillus- and Bifidobacterium mediated antigenotoxicity in the colon of rats. Nutr. Cancer 26, 365–380.

Pronio, A., Montesani, C., Butteroni, C., Vecchione, S., Mumolo, G., et al., 2008. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative colitis is associated with expansion of mucosal regulatory cells. Inflamm. Bowel Dis. 14, 662–668.

Rafter, J., 2003. Probiotics and colon cancer. Best Pract. Res. Clin. Gastroenterol. 17, 849–859.

Reddy, B.S., Rivenson, A., 1993. Inhibitory effect of Bifidobacterium longum on colon, mammary, and liver carcinogenesis induced by 2-amino-3-methylimidazo[4,5-f]quinoline, a food mutagen. Cancer Res. 53, 3914–3918.

Rowland, I.R., Rumney, C.J., Coutts, J.T., Lievense, L.C., 1998. Effect of Bifidobacterium longum and inulin on gut bacteria metabolism and carcinogen-induced aberrant crypt foci in rats. Carcinogenesis 19, 281–285.

Salgado, R., Benoy, I., Weytjens, R., Van Bockstaele, D., Van Marck, E., Huget, P., Hoylaerts, M., Vermeulen, P., Dirix, L.Y., 2002. Arterio-venous gradients of IL-6, plasma and serum VEGF and D-dimers in human cancer. Br. J. Cancer 87, 1437–1444.

Salminen, S., Bouley, C., Boutron-Ruault, M.C., et al., 1998. Functional food science and gastrointestinal physiology and function. Br. J. Nutr. 80, 147–171.

Salminen, S., Gorbach, S., Lee, Y., Benno, Y., 2004. Human studies on probiotics: what is it really proven today? In: Salminen, S., von Wright, A., Ouwehand, A. (Eds.), Lactic Acid Bacteria: Microbiology and Functional Aspects, third ed. Revised and Expanded. Marcel Dekker Inc, New York, pp. 515–530.

Sanders, M.E., 2006. Summary of probiotic activities of Bifidobacterium lactis HN019. J. Clin. Gastroenterol. 40, 776–783.

Sengupta, S., Muir, J.G., Gibson, P.R., 2006. Does butyrate protect from colorectal cancer? J. Gastroenterol. Hepatol. 21, 209–218.

Shahani, K.M., Ayebo, A.D., 1980. Role of dietary lactobacilli in gastrointestinal microecology. Am. J. Clin. Nutr. 33, 2448–2457.

Shu, Q., Lin, H., Rutherfurd, K.J., Fenwick, S.G., Prasad, J., Gopal, P.K., Gill, H.S., 2000. Dietary Bifidobacterium lactis (HN019) enhances resistance to oral Salmonella typhimurium infection in mice. Microbiol. Immunol. 44, 213–222.

Singh, J., Rivenson, A., Tomita, M., Shimamura, S., Ishibashi, N., Reddy, B.S., 1997. Bifidobacterium longum, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. Carcinogenesis 18, 833–841.

Sivieri, K., Spinardi-Barbusan, A.L.T., Barbisan, L.F., Bedani, R., Pauly, N.D., Carlos, I.Z., Benzatti, F., Vendramini, R.C., Rossi, E.A., 2008. Probiotic Enterococcus faecium CRL 183 inhibit chemically induced colon cancer in male Wistar rats. Eur. Food Res. Technol. 228, 231–237.

Soccol, C.R., de Souza Vandenberghe, L.P., Spier, M.R., Medeiros, A.B.P., Yamaguishi, C.T., et al., 2010. The potential of probiotics: a review. Food Technol. Biotechnol. 48, 413–434.

Songisepp, E., Kullisaar, T., Hutt, P., Elias, P., Brilene, T., Zilmer, M., Mikelsaar, M., 2004. A new probiotic cheese with antioxidative and antimicrobial activity. J. Dairy Sci. 87, 2017–2023.

Sultan, A., Durrani, F.R., Suhail, S.M., Ismail, M., Durrani, Z., Chand, N., 2006. Comparative effect of yogurt as probiotics on the performance of broiler chicks. Pak. J. Biol. Sci. 9, 88–92.

Sütas, Y., Soppi, E., Korhonen, H., et al., 1996. Suppression of lymphocyte proliferation in vitro by bovine caseins hydrolyzed with Lactobacillus casei GG-derived enzymes. J. Allergy Clin. Immunol. 98, 216–224.

Tappenden, K.A., Deutsch, A.S., 2007. The physiological relevance of the intestinal microbiota-contributions to human health. J. Am. Coll. Nutr. 26, 679–683.

Urbanska, A.M., Bhathena, J., Martoni, C., Prakash, S., 2009. Estimation of the potential antitumor activity of microencapsulated Lactobacillus acidophilus yogurt formulation in the attenuation of tumorigenesis in Apc(Min/+) mice. Dig. Dis. Sci. 54, 264–273, PubMed:18633708.

Wachtershauser, A., Stein, J., 2000. Rationale for the luminal provision of butyrate in intestinal diseases. Eur. J. Nutr. 39, 164–171.

Weston, S., Halbert, A., Richmond, P., Prescott, S.L., 2005. Effects of probiotics on topic dermatitis: a randomised controlled trial. Arch. Dis. Child. 90, 892–897.

Wilson, R.A., Zolnai, A., Rudas, P., Frenyo, L.V., 1996. T-cell subsets in blood and lymphoid tissues obtained from fetal calves, maturing calves, and adult bovine. Vet. Immunol. Immunopathol. 53, 49–60.

Wong, C.S., Sengupta, S., Tjandra, J.J., Gibson, P.R., 2005. The influence of specific luminal factors on the colonic epithelium: high-dose butyrate and physical changes suppress early carcinogenesis events in rats. Dis. Colon Rectum 48, 549–559.

Xue, H., Sawyer, M.B., Wischmeyer, P.E., Baracos, V.E., 2011. Nutrition modulation of gastrointestinal toxicity related to cancer chemotherapy: from preclinical findings to clinical strategy. JPEN 35, 74–90.

Yeo, S.K., Liong, M.T., 2010. Angiotensin I-converting enzyme inhibitory activity and bioconversion of isoflavons by probiotics in soymilk supplemented with prebiotics. Int. J. Food Sci. Nutr. 61, 161–168.