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Protection against cancer by probiotics: Relevant mechanism and *in vivo* and *in vitro* evidences between 2002 and 2010

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ABSTRACT

Probiotics have been used as alternatives for anti-inflammatory drugs in IBD. Now, more and more scientists are paying increasing attention on probiotics with the effects of anti-carcinogenic. Various mechanisms for their anticancer action have been suggested, particularly in vitro experiment. The involved mechanisms were studied in animal models induced by chemical carcinogen or subcutaneously implanted cancer cell line, such as modulating immune to improve anti-tumor immunological function, altering local metabolic product to affect cell proliferation and apoptosis, regulating harmful enzyme activity to exert a protective effect and so on. As we know, in vivo animal models are designed to mimic the process of carcinogenesis in human, and administrating probiotics to animal models will help us to better understand the underlying mechanisms of the anticancer effect. These animal evidences provide theory basis for clinical trial, and the extensive studies on human provide a convincing base for clinical application of probiotics in cancer treatment. This study will review evidences of cellular, animal model and human study on anticancer effect of probiotics between 2002 and 2010.

KEYWORDS

Probiotics;
Anticancer;
Evidences;
Mechanisms.

INTRODUCTION

Probiotics are defined as 'living microbial supplements that beneficially affect the host animals by improving its intestinal microbial balances'[1]. As we know, the applications of probiotics into a range of dairy products have been well-documented for years, due to their health benefits. In recent years, using probiotics, to improve the condition of patients with inflammatory bowel disease (IBD), has yielded conclusive results. On the other hand, there has been increasing interest in the anticancer effect of probitoics. According to an investigation by Ferlay et al.[2], it showed that, in 2006 in Europe, there were an estimated 3,191,600 cancer cases diagnosed and 1,703,000 deaths due to cancer. The highest incidence was for breast cancer, followed by colorectal cancer and lung cancer. Moreover, the highest mortality was for lung cancer, followed by colorectal, breast and stomach cancers. In light of this, colorectal cancer was ranking the second, whatever incidence or

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mortality. Therefore, promoting the prevention and treatment of colorectal cancer is a matter of great urgency. Not surprisingly, we found that colorectal cancer attracted the most attention by reviewing the studies of probiotics and cancer in recent years. But more and more attention is being paid to the application of probiotics in other cancers.

Cellular evidence

The cellular experiments, using various types of tumor cells to evaluate the anti-carcinogenic effects of probiotics, have been studied over the years. Based on the laboratorial data, many studies have shown promising evidence that well-established of probiotics possess anti-carcinogenic effects, while more and more new strains have been studied for their potential anti-carcinogenic activity. To date, the anticancer activities of probiotics have been profoundly manifested in colon cancer, stomach cancer, lung cancer, hepatocarcinoma and breast cancer cells.

In a study evaluating the effect of the cytoplasm extract from Bifidobacterium bifidum BGN4 (isolated from the feces of healthy human subjects) on human colon cancer cell lines[3], HT-29, HCT-116, and Caco-2 were treated with the polysaccharide fraction (BB-pol), which was extracted from B. bifidum BGN4, at a concentration of 20, 40, or 80μg/ ml for 48 hours. Trypan blue exclusion assay and BrdU incorporation assay showed that BB-pol inhibited the growth of HT-29 and HCT-116 cells (BB-pol at 20μg/ ml inhibited the growth of HT-29 cells by 50.5 ± 3.6%) but did not inhibit the growth of Caco-2 cells. In another study, Ewaschuk et al.[4] conducted a similar research. They assessed CLA (conjugated linoleic acids) which was produced by probiotic strains (0.01 g VSL3 containing L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp bulgaricus, B. infantis, B. breve, B. longum, S. salivarius subsp. Thermophilus.), and found that probiotic strains in VSL3 have the capacity to convert LA to CLA, to up-regulate PPARg, to reduce the viability of cancer cell, and to induce apoptosis in HT-29 and Caco-2 cells. In another study, Lorenzo et al.[5] found that Bifidobacterium longum B12 strain had the ability to adhere to Caco-2 cells and to auto-aggregate. B18 strain showed strongly auto-aggregating and non-adhesive, moreover, B2990 strain showed neither. After 3 hours of B12 and B18 coculture with Caco-2 cells, the result showed that B12 and B18 induced apoptotic deletion of Caco-2 cells, and it was in contrast to B2990. Lee et al.[6] also proved the similar results. They found that incubation of Caco-2 cells with Bacillus polyfermenticus SCD (4.7±0.07 CFU/ml) for 72 h, the adherence percentage of the B. polyfementicus SCD strain was shown to be about 57.5%. Moreover, cell growth was suppressed by 24.6%, 20.3%, 37.1%, and 42.2% after 72 h of treatment with B. polyfermenticus SCD at 100, 500, 1000 and 2000μg/ ml, respectively. In another study conducted by Lee et al.[7], the study was to evaluate the effects of Bifidobacterium adolescentis (isolated from fecal samples of healthy young Koreans) on immunostimulation and anti-proliferation in human colon cancer cell lines. The experiments showed that the butanol extract of B. adolescentis SPM0212 inhibited the growth of Caco-2, HT-29, and SW480 cells by 70%, 30%, and 40%, respectively, at 200μg/mL. Additionally, the butanol extraction induced macrophage activation and significantly increased the production of TNF-α and NO, which regulated immune modulation and were cytotoxic to tumor cells. In recent years, it is assumed that reactive oxygen species (ROS) play a key role in colon cancer[8,9]. Koller et al.[10] developed a model to investigate the prevention of oxidative DNA damage in HT29 cells by LAB strains. The results showed that the impact of LAB(3×10^7 CFU/ml) on DNA damage in HT29 cells was ambivalent: protection towards oxidative DNA damage was observed in the majority of strains (49%), in contrast, certain representatives of species contributed to induced marked DNA damage and increased DNA migration by ROS generating chemicals. In another study, Kim et al.[11] found that Bifidobacterium adolescentis SPM0212 cell free supernatant (200 mg/ml) inhibited the growth of SW480, HT-29, and Caco-2 cells by 32%, 36%, and 47%, respectively, and showed dose-dependent inhibition. Additionally, B. adolescentis SPM0212 exerted an anticancer effect by significantly increased TNF-α, which was derived principally from macrophages and was cytotoxic to tumor cells, production 3380 pg/ml at 200 mg/ml. Thirabunyanon et al.[12] selected Fifty-four strains of lactic acid bacteria obtained from fermented dairy milks to investigate for possible use as probiotics

and for colon cancer biological products. The study showed E. faecium RM11 and L. fermentum RM28 could be used as probiotics and exhibited antiproliferation effect on the growth of colon cancer cells (Caco-2 cells, CLS) by 21-29%, and 22-29%, respectively. Chang et al.[13] conducted a similar job, they assessed a total of 2344 LAB strains isolated from kimchi, Strain KFRI342 displayed the greatest ability to reduce the growth of the colon cancer cells (SNU-C4) by 37.7% at 1.0 mg/ml. In another study, Kim Y et al.[14] found that exopolysaccharides (cb-EPS) isolated from Lactobacillus acidophilus 606 dose- and temporal-dependently inhibited the proliferation of HT-29 cells. Research on mechanism showed that this activity was due to the activation of autophagic cell death promoted, directly by the induction of autophagy-related proteins (Beclin-1 and GRP78), as well as indirectly through the induction of apoptosis-related factors (Bcl-2 and Bak).

While the anti-carcinogenic effect of probiotics towards colon cancer cells has been well-documented, other cancer cells have also gained increasing attention in anticancer of probiotics studies. Kim et al.[15] evaluated the effect of Arginine deiminase (ADI) originating from Lactococcus lactis ssp. lactis ATCC 7962 (LADI) on SNU-1 stomach adenocarcinoma cells. They found that LADI exerted powerful antiproliferative effects, induction of apoptosis and G_0/G_1-phase arrest in SNU-1 cells. In another study, Ma et al.[16] evaluated the anti-carcinogenic effect of Bacillus polyfermenticus (B.P.) on various cancer cells containing human skin cancer cell line A375, breast cancer cell line MCF-7, cervical cancer cell line HeLa, lung cancer cell line A549 and human colon cancer cells (HT-29, DLD-1, Caco-2). The data showed B.P. CM (conditioned medium of B.P. cultures) significantly inhibited proliferation of cancer cells[A375 (88% or 90%), MCF-7 (46% or 86%), HeLa (58% or 39%), A549 (94% or 84%), HT-29 (35% or 56%), DLD-1 (69% or 33%) and Caco-2 (99% or 95%)] when treated for 7 or 14 day, respectively. Furthermore, that exposure of B.P. CM to HT-29 cells for 24 h, 48 h and 2 weeks reduced ErbB2 and ErbB3 expression in both protein and mRNA levels. Moreover, the expression of related factors as cyclin D1 and transcription factor E2F-1 were also decreased by B.P. CM.

Through the above-mentioned studies, in spite of various cancer cell lines, different strains of probiotics, even disparate dose and treat time, the anticancer activity of probiotics had got well affirmative. However, these cellular evidences could not provide an adequate basis for the application of probiotics in human, so further researches as animal model or human study are required.

Animal evidence

The use of animal models to assess the anticancer effect of probiotics and snybiotics has been emphasized for years. Many studies have used rats, mice, hamsters, guinea pigs and turkey to investigate the effect of probiotics. In this review, we will lay a lot of emphasis on the evaluation of anticancer of probiotics in the tumor-bearing rodent models.

Lim et al.[17] conducted a murine subcutaneous model of bladder cancer involving the inoculation of MB49 cells in C57B/L6 mice. The group A (n=8) was fed LGG immediately after tumor implantation, while the group B (n=7) was fed LGG at 1.6×10^8 CFU daily after 7 days. Compared to the controls (which was fed saline), the group A showed a significantly ($P<0.05$) lower tumor size at 35 days after tumor inoculation. The group B had overall smaller tumors than control, but larger tumors than the group A, although the difference in tumor volumes was not significant. In addition, 2 of the 8 mice (25%) in the group A did not develop any tumor. In another study, MEB et al.[18] created a fibrosarcome model in Balb/c mice by subcutaneous implantation of Meth A crystals. Prior to inoculation with tumor cells, mice were fed for two consecutive days with Lactobacillus casei CRL 431 at 1.2×10^9 CFU/day/mouse. They observed that the tumor volume in control (without probiotics, n=25) was about 3.2±0.1 cm^3 on days 30-40 after tumor induction, when the mice died. In probiotic group (n=25), a total of 54±5% of the mice did not present tumor development, while in the remaining 46±4%, a delay of 30 days in the development of the tumor (vol: 1.2±.02 cm^3) was observed. Ohkawara et al[19] evaluated the effect of Butyrivibrio fibrisolvens MDT-1 on aberrant crypt foci (ACF) induction by DMH in Male Jcl: ICR mice. After administration of intact MDT-1 cells (10^9 CFU/dose) 1 and 3 times/week, the numbers of DMH-induced ACF per

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TABLE 1 : Tumor-associated study of probiotic or synbiotic in human

Probiotic strains	Experimental design	subjects	Dose; duration of the study	effects	Ref.
Lactobacillus acidophilus 145 and Bifidobacterium longum 913	A Randomized, controlled &crossover trail	9 women volunteers (aged 22–43 years)	10^9 probiotics per g yoghurt/d (300g/d) for 6 weeks, and controlled diet with the same yoghurt for the following 1 week.	Faecal water obtained from volunteers after intervention with probiotic showed that protected against H_2O_2-induced DNA strand breaks in human colon cancer cells.	26
The synbiotic product: L. rhamnosus GG (LGG)+B. lactis Bb12 (Bb12)+oligofructose-enriched inulin.	A randomised, double-blind, placebo-controlled trial	80 volunteers (43 polypectomised; 37 colon cancer, who had previously undergone 'curative resection' for colon cancer))	encapsulated probiotic bacteria each at 10^{10} CFU and a 10 g sachet of inulin, for 6 and 12 weeks	IL-2 secretion from the polyp group and IFN-γ secretion from the cancer group increased significantly (P＜0·05). Moreover, secretion of IL-10, IL-12 and TNF-a was not influenced by the SYN in either group.	27
Lactobacillus	A Prospective, randomized, non-blinded, controlled trail	202 patients with histological confirmation of superficial bladder and underwent transurethral resection	Control group: 102 received epirubicin ; treatment group: 100 received epirubicin plus daily oral 3×10^{10} cells Lactobacillus casei for 1 year.	The 3-year recurrence-free survival rate was significantly higher in the treatment group than in the control group (74.6% vs 59.9%, p= _ 0.0234),	28
RS-containing high-amylose maize starch (HAMS) +Bifidobacterium lactis	A double-blind, placebo-controlled, crossover trial	13 men and 7 women volunteers(aged 45–75 years)	5×10^9 CFU/d B. lactis LAFTI B94, 25 g /d HAMS; lasted 4 wk without a washout period	This synbiotic supplementation induced unique changes in fecal microflora but did not significantly alter any other fecal, serum, or epithelial variables.	29
Bifidobacterium longum (BB536) and Lactobacillus johnsonii (La1)	A randomized double-blind trial	31 patients undergoing elective colorectal resection for cancer.	A low dose of 10^7CFU/d, a high dose of 10^9CFU/d; Given orally bid for 3 d before operation, and continued postoperatively from d_2 to d_4.	La1 , but not BB536 , adheres to the colonic mucosa, and affects intestinal microbiota.	30
Bifidobacteriu breve strain Yakult	A randomized, single blinded, placebo-controlled trial	42 patients with malignancies admitted for chemotherapy	10^9 of freeze-dried, living BBG-01; started 2 weeks prior to the first day of chemotherapy and continued for 6 weeks.	The frequency and duration of febrile episodes was less in the probiotic group than in the placebo group.	31
Lactobacillus acidophilus and bifidobacterium bifidum	A prospective, randomized, double blinded, placebo-controlled trial	63 patients diagnosed with locally advanced cervical cancer and planned to receive concurrent chemo-radiotherapy	2×10^9CFU/capsule, bid, beginning 7 days before radiotherapy and continuing everyday during radiotherapy.	Grade 2 -3 diarrhea was observed in the study drug group less than in the placebo group (p = 0.002).	32

mouse were reduced by 75% and 40%, respectively. Compared with control group, more pronounced amelioration by intact MDT-1 was noted in the numbers of ACs per mouse. Moreover, the percentage of mice having 3 or 4 ACs per focus was reduced from 70% in the control to 20% after administration with MDT-1 3 times/wk (P < 0.05). Park et al.[20] assessed the effects of Bacillus polyfermenticus on the process of colon carcinogenesis induced by DMH in male F344 rats. 30 rats were divided equally into three groups, and then were fed with either a high-fat and low-fiber diet (control and DMH groups), or a high-fat and low-fiber diet supplemented with B. polyfermenticus (3.1×10^8 CFU/d) (DMH+B. polyfermenticus group). 9 weeks after the initial DMH injections, the total numbers of ACs in the colon were significantly (p < 0.05) decreased in the B. polyfermenticus supplemented group by 40% compared to the DMH group. Lee et al.[6] conducted a similar experimental period of 10 weeks and obtained the same result, although the reduction of ACs was achieved by the supplementation of B. polyfermenticus SCD at 3×10^6 CFU/day. In another study, Matsumoto et al.[21] administered Lactobacillus casei Shirota (LcS) (5.0×10^8CFU/day, 5 days once a week) to 10 Female BALB/c mice bearing colitis-associated cancer via a gastric tube for 20 weeks. The incidence and number of tumors were repressed conspicuously in mice treated with LcS compared with those treated with PBS. A study by Sivieri et al.[22] showed that Probiotic Enterococcus faecium CRL 183 inhibit DMH induced colon cancer in male wistar rats. A total of 30 rats were randomly divided equally into three groups, as Control, DMH and DMH + E. faecium CRL 183(3×10^8CFU/g by gavage daily) group. After 42 weeks, the outcome definitely revealed that a 50% inhibition in incidence in average number of tumors (P < 0.001), reduced the formation of ACF (P < 0.001) and induced the lowest number of adenocarcinoma (P < 0.001) by adding E.

Figure 1

faecium CRL 183. Urbanska et al.[23] conducted a study that male heterozygous C57BL/6 J-ApcMin/+ mice bearing colon cancer received daily oral administration of microencapsulated Lactobacillus acidophilus bacterial cells (10^{10} CFU/ml) in the yogurt formulation, and then sacrificed 9, 9, and 15 animals at weeks 8, 10, and 12 of treatment, respectively. Histopathological analyses revealed fewer adenomas in treated versus untreated mice. Furthermore, treated mice exhibited fewer gastrointestinal intraepithelial neoplasias with a lower grade of dysplasia in detected tumors. In another study, Ma EL et al.[16] created a mouse xenograft model of human colon cancer by subcutaneously injecting the female CD-1 nude mice with DLD-1 colon cancer cells. Four days after the initial cancer cell injection, conditioned medium of Bacillus polyfermenticus (B.P. CM) or conditioned medium of E. coli cultures (E.C. CM) was injected into the peritumoral region every other day until the end of the experiment. After 20 days, data from the mouse xenograft model of human colon cancer cells showed reduced tumor size and weight in B.P. CM-injected mice when compared to E.C. CM -injected mice.

Although many studies have demonstrated convincing anticancer effects of probiotics in animal models, controversial results still existed. Femia et al.[24] used a total of 129 male F344 rats (bearing AOM-induced colon cancer) to assess the anticancer effect of probiotics[Bifidobacterium lactis (Bb12) and Lactobacillus rhamnosus (LGG), each at 5×10^8 CFU/g diet] or synbiotics (a combination of probiotics and the prebiotic inulin enriched with oligofructose). After treatment of 31 weeks, colorectal tumors/rat were 1.9 ± 1.7, 2.2 ± 1.4 and 0.9 ± 1.2 in Controls, PRO and SYN groups, respectively. Rats treated with synbiotics had a significantly lower ($P < 0.001$) number of tumors (adenomas

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and cancers) than control. Interestingly, there was not significant effect of probiotics in reducing tumors (P =0.079). In another study, Le et al.[25] also got the similar result from 180 colorectal cancer-bearing male SD rats. Results after 26 weeks treatment, the differences were marked ($P < 0.01$), the incidence and multiplicity of colonic neoplasm in rats, which were fed with the carbohydrate 'resistant starch' (RS) in combination with Bifidobacterium lactis (1×10^{11} CFU/g), were significantly reduced by >50%, whereas no protection against cancer was observed in the group supplemented with only B. lactis.

There may be various factors contribute to such controversial findings. For instance, it due to characteristics of different probiotics, effective dose of probiotics, The timing of initiation and duration of probiotics treatment, compositions of diets, sample size, and other human elements in the whole process. In spite of that, probiotics can be used as a promising agent alone or combined with prebiotics as synbiotics in anticancer therapy.

Human evidence

The anticancer effect of probiotics not only has been well-documented in cellular and animals models, tumor-associated researches in human have also gained over the years, as shown in TABLE 1.

Mechanism of anti-carcinogenic effects *in vivo*

Until now, a number of studies in vivo have been conducted to study mechanisms proposed for the protective effects of probiotics or synbiotics. Those suggest that the anticancer mechanisms of a certain probiotic bacterium would not be same in different types of tumors. Researches about colon cancer have attracted the most attention. The possible mechanisms are shown in figure 1.

In respect of immune modulation, numerous studies[17-19,21-23,27,30,33] were concern about that. In these studies, researchers evaluated the changes of immune cells or the levels of cytokines by probiotic, which involved in anticancer effects of probiotics in vivo. Take for example, enhanced the immune response with increased numbers of NK and NKT cells or Dendritic subsets for CD83-123, CD83-11c or CD83-HLADR, in addition, exerted tumor-suppressive effects with an inhibition of IL-6 production or increasing IL-4, IFN-γ and TNF-alpha. It is well established that IL-6 signaling is important for the pathogenesis of colon cancer, breast and lung cancer[34-36]. Moreover, IFN-γ is important in the host defense against tumors[37], IL-4 exerts the ability of control over the inflammatory response induced by the carcinogen[38], and TNF-alpha possessed the prominent function of anticancer immune responses[39].

The other suggested mechanism includes inhibition of harmful enzyme activity by probiotics, such as Ohkawara et al.[19] and Kim et al.[11] found that administration with probiotics suppressed precancerous Lesions formation by inhibiting β-glucosidase, β-glucuronidase, tryptophanase, and urease activity of colon bacteria. The mechanism of protect against genetic damage was proposed by Park et al.[20] and Oberreuther-Moschner et al.[26]. Some studies[6,29,30] showed that based on the characteristic of adherence, probiotics affected intestinal microflora to exhibit the anti-tumor effect by reducing the concentration of pathogens or binding of mutagens[40]. In another study[4], the anti-carcinogenic mechanism of probiotic bacteria to exert effects through the production of CLA was confirmed, since CLA, a ligand for the peroxisome PPARγ, could repress growth of colon cancer cells[41], and CLA also suppressed cellular proliferation and induced apoptosis by reducing the mRNA ratio of Bax/Bcl-2 in colonic mucosa of rats[42].

Although the numerous mechanisms responding for anticancer effect by probiotics were verified by some vivo studies, further studies are needed to make a better comprehending of the mechanisms and better formulations for human consumption.

CONCLUSIONS

Probiotics have been widely evaluated for the effect of anticancer in cancer cell lines, animal models and humans. Although certain strains of probiotics didn't exhibit anticancer activities, when they combined with some types of prebiotics simultaneously as synbiotics, and also could exerted a protective effect against cancers. In order to promote the clinical application of probiotics, numerous of researches were carried out to explore the mechanisms of the anticancer activities. Several hypothetic mechanisms were suggested and

proved, but it is far from enough. Thus, more researches are needed to investigate the role of probiotics in the process of oncogenesis and corresponding mechanism, which will establish the foundation for the clinical application of probiotics in prevention and treatment of tumor.

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