Potential effect of probiotics in the treatment of breast cancer

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Abstract

Breast cancer is one of the most important causes of cancer-related morbidity and mortality in the world. Probiotics, as functional food, have the potential to act against breast cancer, as evidenced by cell-based and animal model experiments. Probiotic may be useful in prevention or treatment of breast cancer by modulating the gastrointestinal bacteria and the systemic immune system. However, large-scale clinical trials and intensive research are mandatory to confirm the *in vitro* and *in vivo* results and exploring the probiotics-related metabolic, immune, and molecular mechanisms in breast cancer. This current review summarizes the available data related to probiotics and their potential role in the treatment of breast cancer.

Introduction

Breast cancer (BC) is the most frequent cancer in women, the second most common cancer worldwide, and the second primary cause of cancer-related deaths.[1] One in eight women who live to age 85 years will develop BC over the course of their lifetime.[2] Gastrointestinal (GI) tracts of humans and animals contain a complex community of bacteria, which has a deep interaction with host mucosal epithelial cells and immune cells in a bidirectional fashion.[3] These microorganisms are helpful in physiologic activities such as digestion, metabolism, they metabolize bile acids and synthesize vitamins B and K, while their antigens and their metabolic products can stimulate production of cytokines against potential pathogens.[3] The composition of the GI bacteria is highly dynamic, and internal or external factors can influence this population growth including age, race, diet, maternal colonization, international travel, infections and pharmaceuticals.[4,5] Therefore, the bacteria composition and complexity tend to change in numbers and strains from the proximal to the distal GI tract during the lifetime. GI bacteria also play a crucial role in the development of homeostasis of the innate and adaptive immune system, and an alteration of its composition contributes to various diseases including metabolic disorders such as obesity and type 2 diabetes, autoimmune diseases such as rheumatoid arthritis, immune-related diseases such as atopy and asthma, and other disorders such as inflammatory bowel disease, irritable bowel syndrome and cancer.[6-10] Epidemiological studies have shown an association between the overuse of antibiotics and an increased incidence of extra-colonic neoplasms, including BC, indicating that GI bacteria has a role in the carcinogenesis of local and distant tumors.[11,12] Latest studies have reported that certain bacteria may improve the efficacy of some traditional anti-neoplastic drugs[13] and of immunotherapies.[14] The aim of this review was to compile the available information about the potential benefit of probiotics, modulating the GI bacteria and systemic immune system, in the treatment of BC.

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Probiotics and cancer

The term *probiotics* has been used for several years, and their immunomodulatory effects were postulated by Nobel prize laureate Élie Metchnikoff over 100 years ago.[15] Probiotics (bacteria or yeasts) were defined by the Food Agricultural Organization (FAO) and the World Health Organization (WHO) as live microorganisms which when administered in adequate amounts (in food or as a dietary supplement) confer a health benefit on the host.[16] The most commonly used bacterial strains for probiotic purposes are the lactic acid bacteria, which are mainly consumed as fermented dairy products such as yogurt. Studies have shown that about 10-30% of probiotics survive in the GI tract, depending on a number of variables, including the type of probiotic[17,18] and their resistance to acid pH and biliary acids to colonize the intestine.[19] Probiotics have been found to reduce absorption of harmful mutagens that may contribute to the colon carcinogenesis[20] or reducing the number of β-glucuronidase-expressing bacteria that transform pre-carcinogens into active carcinogens.[21-27] In fact, several mechanisms have been proposed how probiotics may inhibit colon cancer; these include: enhancing the host's immune response, altering the metabolic activity of the intestinal microflora, binding and degrading carcinogens, producing antimutagenic compounds, and altering the physiochemical conditions in the colon.[28] Probiotics have been tested in animal tumor models confirming their ability to prevent colon cancer.[29,30]

GI bacteria and its role in the breast cancer tumorigenesis

GI bacteria plays an important role in the modulation, reabsorption, enterohepatic circulation, and modulation of

systemic estrogens.[31-33] The GI bacteria has an association with estrogen levels through secretion of β-glucuronidase, an enzyme that deconjugates estrogen to its free, biologically active form available for tissue uptake. The increase in the amount of free estrogens for reabsorption contributes to the risk of development of hormone-driven malignancies such as BC.[34] Interestingly, β-glucuronidase prevalence was also found in the nipple aspirate fluid of BC survivors.[35] Data on the role β-glucuronidase and other fecal enzymes in BC risk are yet limited.

Diet, alcohol, and cholesterol metabolism, which are some risk factors associated with BC, have a direct influence on the GI bacteria and *vice versa*. Changes in the diet are known to affect the overall GI bacteria composition and function.[36] Strict vegetarians have increased fecal excretion of conjugated estrogens compared with non-vegetarians, leading to decreased plasma estrogen concentrations and protect against subsequent BC risk. The activity of β-glucuronidase is also significantly lower in the vegetarians than in the omnivores.[37,38] A strong association has been reported between the GI bacteria composition and the variation of blood lipid levels.[39] Hypercholesterolemia is a risk factor for ER-positive BC.[40] Cholesterol metabolite 27-hydroxycholesterol (27HC) has been shown to possess estrogenic activities and to promote breast tumor growth in xenograft mouse models.[41] In humans, hypercholesterolemia and its role in breast carcinogenesis remains to be defined.[42,43] Several small-scale studies reported lowered cholesterol on using probiotics, which may support their benefit in blocking the hypercholesterolemia-estrogen cancer mechanism.[44,45]

Alcohol consumption alters the composition of the colonic microbiome in rats.[46] There is an extensive information alcohol consumption increases the risk of ER-positive BC in postmenopausal women.[47-51] A recent study showed a positive association between alcohol consumption and endogenous estrogen levels and mammographic density in premenopausal women.[52] Similarly, alcohol intake after BC diagnosis is associated with both increased risk of recurrence and death.[53] Both GI anaerobic and aerobic bacteria are present at higher levels in subjects with chronic alcohol abuse and alcoholic cirrhosis compared with healthy controls.[54-56]

The role of GI bacteria in estrogen deconjugation and the influence of women lifestyle seem to be contributors to the breast carcinogenesis. However, these observations need further study and more detailed definition.

Effect of probiotics against BC *in vitro* and animal studies

Numerous *in vitro* and animal studies have been carried out to investigate the effect of probiotics against BC. Table 1 shows some examples of these *in vitro* studies.[57-64]

Several studies in animals have shown the benefit of probiotics against BC. Oral administration of *Lactobacillus acidophilus* in 0.5 mL suspension containing 2.7×10^8 CFU/mL was given every day starting from two weeks before BC tumor transplantation and continued 30 days after with 3 days intervals. The results showed a significant increase in the survival time among the *L. acidophilus* group compared to that of the controls, demonstrating that this treatment can promote the immune responses via stimulation of the production of pro-inflammatory cytokines such as IFN-γ and inhibition of the production of anti-inflammatory cytokines such as IL-4 and IL-10.[65] Additional animal studies confirmed that oral administration of *L. acidophilus* displays anticancer activity in mice bearing breast tumors.[66]

In another study, 0.5 mL of this suspension containing 2.7×10^8 CFU/mL *Lactobacillus casei* was orally administered to mice using a standard gastric feeding tube. The suspension was given

Table 1. Examples of i*n vitro* anticancer effect of probiotics in breast cancer cells.

Probiotic stain	Cell line tested	Treatment and Duration	Results	Ref
Enterecoccus lactis IW5	MCF-7	Incubation with EL metabolites for 24 h	30% cell inhibition	57
Lactoccocus lactis NK34	MCF-7	Inoculation of 10^5 or 10^6CFU/well of bacteria, incubated for 44 h	59% and 98% cytotoxic effect at 10^5 and 10^6CFU/well, respectively	58
Lactococcus lactis KC24	MCF-7	Inoculation of 10^5 or 10^6CFU/well of bacteria, incubated for 48 h	Strong cytotoxic effect toward cancer cells	59
Enterococcus faecalis and	MCF-7	Incubation of 25, 50, 100 and 200 µg/mL	Significant inhibition of cell proliferation,	60
Staphylococcus hominis		of live, heat killed cells or cytoplasmic fractions of bacteria for 24, 48 or 72 h	induction of apoptosis and cell cycle arrest	
Lactobacillus crispatus and *Lactobacillus rhamnosus*	MCF-7	Incubation and supernatant of various concentrations	Cytotoxic effect towards cells, together with suppression of hypoxi-inducible factor (HI)-1 pathway	61
Kefir grains water 50 mg/mL (mix of *Lactobacillus acidophilus, Lactobacillus casei*, and *Lactococcus lactis*	4T1	MTT assay	The IC_{50} values after 48 h and 72 h were 12.5 and 8.33 mg/mL, respectively	62
Lactobacillus plantarum	MDA-MB-231	Various concentration	Apoptosis was mediated by downregulation of the NFκB pathway	63
Lactobacillus crispatus and *Lactobacillus acidophilus*	MDA-MB-231	MTT assay	Antiproliferative activity; lactobacilli can decrease transcriptional activity of four different cancer-testis antigens	64

MTT assay; [3-(4,5-dimethylthiazol-2-y-2,5-diphenyltetrazolium bromide] assay.

daily for two consecutive weeks before subcutaneous transplantation of adenocarcinoma breast tumor into mice. The administration then continued for three weeks with a 3-day interval between each week. Data analysis showed a significant decrease in the growth rate of tumors and the survival was significantly prolonged compared to the controls. The study has concluded that oral administration of *L. casei* can affect stimulation of the Th1 cytokine production in mouse spleen cell culture and NK cell cytotoxicity.[67]

Oral administration of fermented milk containing *Lactobacillus helveticus* R389 demonstrated an immunoregulatory response in BC-bearing mice and suggested its use as immune adjuvant therapy to protect against malignancies.[68] In mice treated with selenium nanoparticles enriched with *Lactobacillus plantarum*, an increase of IFN-γ and IL-2 levels was reported, but the animals also showed enhanced NK cell activity.[69] Furthermore, oral administration of selenium nanoparticles enriched with *Lactobacillus brevis* seemed to be related with better disease prognosis among highly metastatic breast tumor-bearing mice.[70]

A Slovakian group demonstrated the chemopreventive efficacy of a new probiotic bacterial strain, Lactobacillus plantarum LS/07, in a rat model of BC. Mammary carcinogenesis was induced by 7,12-dimethylbenz[a]anthracene (DMBA). Lactobacillus plantarum LS/07 (at a dose of 8.4×10^8 CFU/rat) was administered daily before the first DMBA dose and given until the end of the experiment (16 weeks). The treatment with the probiotics significantly suppressed the tumor frequency, increased Cd4+T-cells in tumor tissue, and reduced the serum tumor necrosis factor (TNF)-α concentration and the level of Cd8+ T-cells in the blood while increasing their number in tumor tissue.[71]

A natural product, Kefir, is a unique cultured product that contains beneficial probiotics. Kefir grains contain various kinds of microbial flora, including the most commonly studied species with probiotic potential such as *L. acidophilus, L. casei,* and *Lactococcus lactis*.[72,73] In another animal experiment, the kefir grains were fermented for 24 h at room temperature. After that, the grains were filtered out from the fermented medium. Mice with tumors were fed orally with kefir water (150 mg/kg body weight per day). All mice in the tumor group were inoculated with 1×10^5 4T1 triple-negative 4T1 murine BC cells subcutaneously, and treatment was administered orally on the same day as the tumor inoculation for 28 days. The tumor size in kefir water-treated mice was smaller than that in untreated mice. The tumor weight and volume were also reduced significantly by 29.53% and 32.92%, respectively, in kefir water-treated mice as compared to the untreated mice. Kefir water exhibited antimetastatic and antiangiogenesis effects in 4T1 cell-challenged mice *in vivo* through reducing 4T1 cell mitosis, promoting apoptosis, modulating immune systems, inhibiting inflammation in the tumor microenvironment, and regulating angiogenesis-related proteins and genes.[74]

Clinical trials

Probiotics in a colon cancer clinical trial has shown a benefit for post-operative complications, therapy-related toxicity and improving the quality of life.[75] Recently, a cohort study with 12-year follow up of 45,241 volunteers determined that high yogurt intake (*Streptoccocus thermophilus* and *Lactobacillus delbrueckii*) was significantly associated with decreased colon cancer risk.[76] Probiotics have also shown the ability to prevent the recurrence of superficial bladder cancer.[77]

In vitro and *in vivo* studies have provided evidence that probiotics display activity against BC. However, only a few clinical trials have been done in these patients. In a Japanese population-based case-control study, 306 cases with BC and 662 controls aged 40 to 55 years were investigated about their diet, lifestyle, and other BC risk factors using a self-administered questionnaire and interview. It was concluded that regular consumption of *L. casei* Shirota and soy isoflavones since adolescence was significantly associated with decreased BC risk in Japanese women.[78] Therefore, long-term exposure was required to accomplish a chemopreventive effect on cancer development.

The clinicaltrial.gov web page has registered just two ongoing clinical trials studying the benefit of probiotics in BC patients. The first trial, NCT03358511, is a single experimental arm studying the number of cytotoxic T lymphocytes (CD8+ cells) in BC subjects treated with probiotics. Twenty post-menopausal BC subjects will be given 2-4 weeks of probiotics prior to surgery in operable stage I-III breast adenocarcinoma tumors ≥1.0 cm. Subjects will take the probiotics three times a day. The probiotic under study is Primal Defense® ULTRA (Garden of Life LLC, USA), which is an over-the-counter probiotic that provides 15 billion colony-forming units of 13 species of beneficial bacteria. The second study, NCT03760653, is a randomized controlled pilot study to determine the effects of physical exercise together with supplementation of a probiotic on the GI bacteria balance, GI immune system and the quality of life in 30 BC survivors. BC survivors will be randomly assigned to each of the three groups: i) probiotic supplementation + supervised combined physical exercise; ii) probiotic supplementation and habitual sedentary lifestyle; and iii) a control group following the usual lifestyle and receiving a placebo. The two supplemented groups will take three capsules (*Lactobacillus rhamnosus, Lactobacillus paracasei, Lactobacillus acidophilus, Bifidobacterium bifidum*) a day (at night before bedtime) for 12 weeks.

So far, there is just a few already executed or running clinical trials testing probiotics in BC patients, and no prospective studies about the efficacy of probiotics in the BC prevention or treatment have been planned.

Conclusions

Oral probiotics display a vast range of beneficial properties and have gained an increasing medical importance over the last decade. Presently, it is believed that many of the commercially available probiotic products are safe to use and have beneficial health effects for the host. In this paper, we have reported the potential of oral probiotics against BC confirmed by human BC cell-based and animal experiments. The results on animal studies indicate that probiotics may have an anticancer systemic property, enhancing the systemic immune system, useful for interventions to prevent and control progression of BC. Although, other different mechanisms may be involved in these beneficial effects, mainly due to the modulation by the GI bacteria and subsequently the suppression of carcinogenesis in the breast. More clinical research from the academia and industry is necessary to establish the value of probiotics and understanding of their immune mechanisms in the prevention and treatment of patients with BC. There is a road ahead to identify the bacterium or bacteria strains active against to the malignancy, the probiotics dosages and treatment schemes may bring a benefit for different BC types, stages and settings.

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