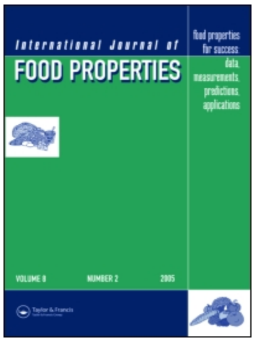

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Anticarcinogenecity of microbiota and probiotics in breast cancer

Saima Shakil Malik[a,b], Ayesha Saeed[a], Mehreen Baig[c], Naveed Asif[b], Nosheen Masood[a], and Azra Yasmin[a]

[a]Department of Environmental Sciences, Microbiology and Biotechnology Research Lab, Fatima Jinnah Women University, Rawalpindi, Pakistan; [b]Surgery Department, Armed Forces Institute of Pathology, Rawalpindi, Pakistan; [c]Chemical Pathology and Endocrinology, Fauji Foundation Hospital, Rawalpindi, Pakistan

ABSTRACT

Breast cancer is one of the most important causes of cancer related morbidity and mortality in the world. Along with genetic, environmental factors also play a multifaceted role in the development of disease. Breast contains several bacterial species performing specialized functions. Probiotics, as functional food, play pivotal role against breast cancer development *in vivo* and *in vitro*. Current review summarized all the available data related to diet, probiotics, and their association with breast cancer risk along with underlying mechanisms. Presently, it was believed that many of the commercially available probiotic products were safe to use and had some beneficial health effects for the host. Probiotics had a potential to act against breast cancer progression evidenced by many animal model and cell-based experiments. Some probiotics strains may be useful as an adjuvant therapy for breast cancer prevention or treatment, by modulating immune response or breast microbial community. However, large-scale clinical trials and intense research are mandatory to explore probiotics-related metabolic and molecular mechanisms in breast cancer.

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Adjuvant therapy; Bacteria; Breast cancer; Cancer prevention; DNA damage; Immune Response; Probiotics

Introduction

Breast cancer is the most common malignancy among women and accounts for 29% of cancer cases diagnosed in women. According to an estimate, approximately 2.5 million breast cancer cases were registered in 2016.[1] Diverse variations in breast cancer incidence was thought to be outcome of differences in hormonal factors, reproductive patterns, and detection strategies at different stages.[2,3] Advancement in the screening and treatment of breast cancer have steadily decreased its mortality particularly for HER-2 and luminal cancers but for triple negative cancers, it remains at higher rates.[4] However, regardless of this extensive progress, all the ethnic/racial groups have not been equally benefitted because of number of reasons including stage distribution among patients, ethnic rate of survival, and mortality.[1,5] Environmental and genetic factors together involve a complex interplay in breast cancer etiology. Older age at menarche, greater parity, younger age at the first birth, and long breast-feeding duration were associated with decreased risk of breast cancer.[4,6,7] Whereas alcohol consumption, high glycemic diet, higher body mass index, familial history of breast cancer, menopause age, and menopausal hormonal therapy were established risk factors for breast cancer.[8–11]

Diverse microbiota is associated with several human body parts such as gastrointestinal tract, mouth, and skin. The composition of this microbiota chiefly is bacteria, though, fungi, viruses, and protozoans also exist.[12] Human microbiota consists of enormous species of bacteria and majority of them are beneficial to the host. Some of them prevent pathogens to clink with gut wall and preserve immunity of gut mucosa.[13] In large intestine of humans, gut microbiota is in abundance approximately one hundred billion organisms per intestinal content gram.[14] Number of gut bacteria exceed

CONTACT Saima Shakil Malik saimamalik25@yahoo.com Fatima Jinnah Women University, The Mall, 46000 Rawalpindi, Pakistan
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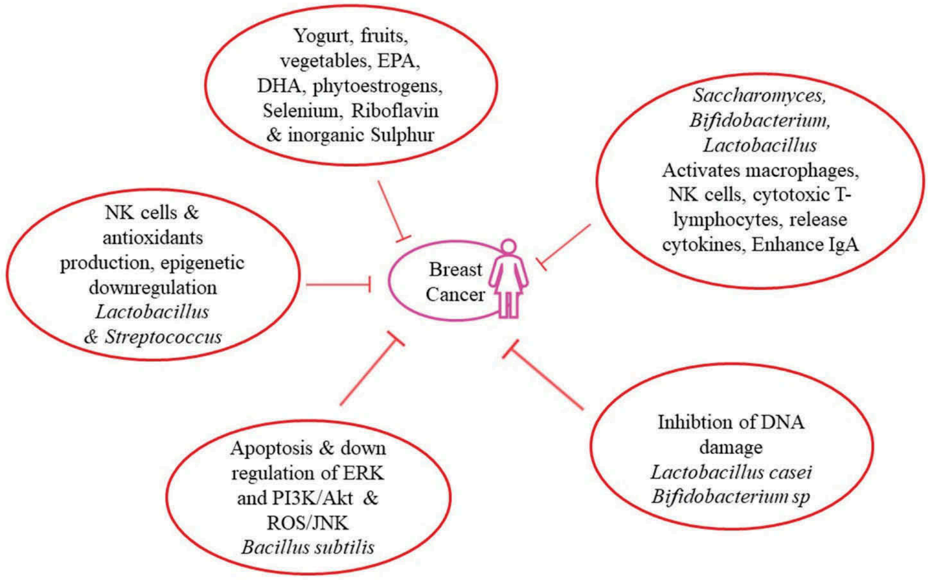

Figure 1. Anticarcinogenecity of probiotic microbiota in breast cancer.

the total number of host's eukaryotic cells and impart various health benefits.[15] This gut flora mainly consists of probiotic bacteria and migrates to other parts of body especially in breast of lactating females but the transport mechanism from gut to breast is still unknown.[16]

Probiotics means "for life" or an antonym for antibiotics [17], when taken in sufficient amount, viable and non-disease causing microorganisms (bacteria or yeasts) impart health benefits via preclusion (prevention) and cure of particular pathological disorders or can lessen the possibility of disease to host are referred as probiotics.[18,19]

Various microorganisms are used as probiotics especially lactic acid bacteria (LAB). LAB includes most of *Lactobacillus* species, some species of *Bifidobacteria, Enterococcus*, and *Streptococcus*.[20] A non-LAB probiotic, i.e., *Escherichia coli* Nissle 1917, was established to be operational in the treatment of infectious intestinal disorders.[21] Most of these bacterial species reside in human intestine.[15] The only probiotic yeast employed is the nonpathogenic *Saccharomyces boulardii*.[22,23] LAB and certain non-LAB probiotics are generally recognized as safe organisms which can be securely used for medical or veterinary purpose.[24]

Numerous aspects of biological function are controlled by usual gut microflora including cancer prognosis.[25] Normally, probiotic bacteria are like natural inhabitants (bacteria) of the human gut specifically those of breastfed infants that are showing natural fortification against a number of diseases and infections.[12] There are vast, evidences that support effectiveness of probiotics for different illness including antibiotic associated diarrhea, traveler's diarrhea, ulcerative colitis, Cohn's disease, etc. Abdominal cramps, flatulence, bloating, and watery diarrhea could be the result of incomplete lactose absorption by gut wall. This occurs due to lactase reduction (β-galactosidase) in intestinal mucosa and might be cured by probiotics (LAB) resulting in lactase production.[12]

Health benefits derived from probiotic food intake (LAB fermented food, probiotic drinks, etc.) containing *Lactobacillus* spp., *Enterococcus* spp., *Bifidobacterium* spp., and *Lactococcus* spp., etc. are documented.[26–42] Numerous health benefits related to probiotics consumption are explored but its involvement in the breast cancer etiology is still not fully understood. Therefore, current study is designed to explore the association of probiotics with risk of breast cancer, as illustrated in Fig. 1.

Diet and breast cancer

Various epidemiological studies in animals and human have reported a well-established role of diet in breast cancer prevention or development.[43,44] Diet is one of the most modifiable breast cancer risk factor. Changes in the dietary habits not only related to reduced cancer risk but also patients already diagnosed and treated with breast cancer can improve their overall health and increase survival rate by opting healthier diet and better life style.[45] Many studies have provided evident that obesity and breast cancer are linked with each other.[46] Being overweight means a person is at a risk of having breast cancer. Diet rich in glycemic load was significantly associated with increased risk of breast cancer.[11] Certain approaches can help to prevent weight gain that might not only decrease breast cancer risk but also improve treatment outcomes in breast cancer patients.[47]

Several studies suggested that intake of omega-6 and omega-3 particularly marine fatty acids, i.e., eicosapentaenoic and docosahexaenoic was linked with better breast cancer prognosis.[43,48,49] *In-vitro* inhibition of cancer cells and reduced tumor growth in breast cancer rat models by canola oil suggested its inverse relationship with breast cancer progression.[50,51] Intake of vegetables and fruit rich diet was positively associated with reduced breast cancer risk.[52] It was well documented that yoghurt consumption was negatively associated with breast cancer risk.[12,53]

Dietary fiber intake was also associated with decreased risk of breast cancer. It was reported that dietary phytoestrogens can increase ERα positive breast cancer risk, and it was linked with their estrogenic effects illustrated *in vivo* and *in vitro*. The proliferative consequence of soy isoflavones was primarily experienced in tumor bearing animal models. But inconsistently, phytoestrogens ingestion has also been associated with decreased breast cancer risk.[54] Controversy related to soy isoflavones effect on risk of breast cancer was investigated and it was confirmed that soy isoflavone phase II metabolism is different between rodents and humans. Therefore, it should be considered important whether to use results obtained from rodents for humans or not. Soy consumption is associated with reduced breast cancer risk among Asians.[55] Researchers are interested to explore the exact hormonal and non-hormonal isoflavones mechanism by which they can exert some beneficial effects. Soy isoflavones shared similar chemical structure with estrogens and considered as probable selective estrogen receptor modulators.[56] So, they can mimic estrogen and bind to estrogen receptors and stimulate or inhibit its functions in tissues. Montales et al., using estrogen receptor-negative and receptor-positive human breast cancer cells, reported that sera of mice ingesting a diet containing blueberry polyphenol and isoflavone genistein changed mammosphere formation.[57] Breast cancer prevention by genistein was linked with regulation of breast adiposity.[58]

Role of folate or folic acid is still controversial and is investigated both in animal models and breast cancer patients. Some of the epidemiological studies showed inverse relationship between folic acid consumption and breast cancer risk.[43,59] It was observed that useful effects of folate are associated with a genetic polymorphism of MTHFR (folate-metabolizing enzyme, methylenetetrahydrofolate reductase) in some populations. Different studies have reported that *MTHFR C677T* polymorphism might be able to modify the association between risk of breast cancer and dietary intake of folic acid.[60–62] A systematic review illustrated that European and American women are at greater risk of breast cancer because of increased consumption of folate or folic acid in the form of fortified foods.[63]

Selenium, essential micronutrient, was investigated to be inversely associated with breast cancer risk in animal models.[64] Riboflavin was also reported to be associated with reduced risk of breast cancer.[65] Inorganic sulfur showed markedly decreased proliferation of human breast cancer cells due to reduced ErbB2 and ErbB3 mRNA expression and protein, stressing ErbB-Akt pathway.[66] There is still a need to do more work in order to investigate the association of diet with breast cancer risk and fulfil the gaps.

Association of bacteria with breast cancer

It was reported that health encouraging bacteria, *Lactobacillus* and *Streptococcus*, are more predominant in healthy breast than the cancerous one. Both these bacterial groups possess anticarcinogenic properties, i.e., they involved in the production of natural killer (NK) cells to regulate tumor progression. Immune cells reduction is directly linked with increased breast cancer risk. Antioxidants produced by *Streptococcus thermophilus* are linked with decreased DNA damage, and thus, cancer by neutralizing reactive oxygen species (ROS).[18]

In healthy breast, *Lactococcus* and *Streptococcus* bacteria are more prevalent because bacteria were thought to have anticancer property. Bacteria from cancerous females were grown on human breast cancer cells to check their ability of triggering DNA damage. Proliferation of these cancerous cells showed alarming situation of double-stranded DNA breaks caused by three different bacterial strains, i.e., *Enterobacteriaceae, E. coli*, and *Staphylococcus*. Probiotic bacteria, *Lactobacillus*, can break down carcinogens. Antioxidants that decrease DNA damage are produced by probiotic strain *S. thermophilus*.[67]

Kinjo et al.[68] working with association of microbial dysbiosis with breast cancer reported that normal breast tissue was enriched with *Sphingomonas yanoikuyae* as compared to the diseased one, suggesting its potential role as a probiotic. Remarkably, *S. yanoikuyae* exhibit glycosphingolipid ligands, dynamic activators of iNKT (invariant NKT) cells. iNKTs are central mediators in cancer immunosurveillance and have fundamental role in controlling breast cancer metastasis.[69,70] Future studies are aimed to explore *S. yanoikuyae*'s prospective role in the development and progression of breast cancer.

Lactobacillus crispatus and *Lactobacillus acidophilus* were reported to have antiproliferative activity against breast cancer cells. Additionally, lactobacilli can decrease transcriptional activity of four different cancer-testis antigens. It was reported that expression of cancer-testis antigens involves epigenetic regulations. Therefore, lactobacilli may cause epigenetic downregulation of this expression. Expression of cancer-testis antigens was linked with poor prognosis and high-grade tumors, so expressional downregulation by lactobacilli may open up new era of clinical research applications.[71]

Enzyme activity

Bacillus subtilis CSY191, a potential probiotic and biosurfactant (surfactin) producer, was isolated from doenjang, (traditional fermented soybean paste of Korean origin). Surfactin hinders MCF-7 growth in dose dependent manner. Apoptotic induction and cell cycle arrest through the down-regulation of ERK and PI3K/Akt (cell survival regulating signals) are responsible for this growth hindrance via surfactin. Surfactin induces apoptosis and stop proliferation of MCF-7 human breast cancer cells through mitochondrial/caspase ROS/JNK-mediated pathway. Production of ROS caused by surfactin induce regulation of stress-induced apoptosis through activation of ERK1/2 and JNK. Apoptotic cell death induction is a promising approach for cancer treatment.[72]

Cytotoxicity

It was reported that tumor development was delayed and sometimes blocked as well when a mouse with breast cancer was given fermented milk containing probiotic bacterium *Lactobacillus casei* (CRL 431). It was associated with tumor triggered modulation of immune response. Immune response can be improved by daily intake of probiotic strain *L. casei*, thus decreasing tumor growth and increasing endurance.[12,73]

Reduced NK cells and their cytotoxicity were correlated with cancer development. Different probiotic bacteria have ability to enhance NK cell activities. Three weeks consumption of fermented milk containing *L. casei* was reported to elevate the activity of NK cells in aged people and disappeared after 6 weeks.[74] Number of NK cells were restored to original in smokers simply by 3 weeks daily intake of *L. casei*.[75] Therefore, probiotics positively effects NK cells functioning. But with the passage of time, probiotics efficiency seem to decrease, gathering scientist's attention.[76]

Oral administration of fermented milk with *Lactobacillus helveticus* R389 demonstrated immunoregulatory response in breast cancer bearing mice and suggested its use as immune adjuvant therapy to protect against malignancies.[77] Yazdi et al. not only reported an increase in inferon (IFN)-γ and IL-2 levels but also shows enhanced NK cell activity in selenium nanoparticles enriched *Lactobacillus* *plantarum*-treated mice. These results illustrated that this administration modulated immune responses. IFN-γ/IL-4 rise upon administration of selenium nanoparticles enriched *L. plantarum* may highlight a Th1 bias of immune response. Reduced tumor growth along with increased survival rate in 4T1 breast cancer mice model showed that selenium nanoparticles enriched *L. plantarum* may persuade a more effective antitumor response among them.[78] Furthermore, oral administration of selenium nanoparticles enriched *Lactobacillus brevis* is suggested to be related with better disease prognosis among highly metastatic breast cancer bearing mice.[79]

Other studies also reported similar kind of results in breast cancer bearing mice that administration of *L. acidophilus* altered cytokine production in a Th1 protective manner, promising antitumor immunity. Therefore, there is a possibility to use *lactobacilli* or other probiotic microorganisms as adjuvant treatment in anticancer chemotherapy.[80,81] To date, data representing correlation between probiotics and NK cells are quite insufficient, therefore, advanced studies are still required to explore the underlying mechanisms.

Reduction of DNA damage by probiotics

Cell susceptibility to DNA damage and capability for restoring this damage is essential for cancer induction, elevation, and evolution. Increased DNA damage was observed in breast cancer patients as compared to normal healthy controls.[82,83] BRCA1, PTEN, and TP53 genes are involved in DNA repair mechanism but any alteration would lead to increased breast cancer risk.[84–86] Loss of heterozygosity, followed by loss of expression of genes for DNA damage response or alteration of cell cycle control, results in inherited breast cancer in pre-menopausal years.[83,85,86]

In-vivo and *in-vitro* studies showed that certain probiotics procured with antigenotoxic activity. *L. casei* Shirota inhibits DNA damage in the rat model on exposure to mutagen (*N*-methyl-*N*-nitro, *N*-nitrosoguanidine).[87] Different lactobacilli species showed antigenotoxicity in rats against 1,2-dimethyl hydrazine (carcinogen) in specie specific manner. *L. acidophilus* when treated with heat lost antigenotoxic effect thus showing viable organism as a liability. *In-vitro* studies showed antimutagenic activity of consortium of probiotic strains including *E. coli, L. casei*, and *Bifidobacterium longum*.[88] DNA damage was expressively reduced by *Bifidobacterium* sp. *420, Bifidobacterium Bb12, Enterococcusfaecium*, and *Lactobacillus bulgaricus. Bifidobacterium Bb12* was highly defensive against DNA damage. Incubating the different concentrations of *Bifidobacterium Bb12* and *L. plantarum*in faecal water showed reduced genotoxicity. Heat-treated (nonviable) probiotics had no effect on faecal water genotoxicity.[89]

It was thought that breast cancer risk can be reduced in perimenopausal women with probiotic supplementation. But it was reported that short-term probiotic and soy supplementation did not have distinct effect on the hormonal profile of these women.[90] Combined long-term exposure of *L. casei* and soy milk proved to be beneficial in breast cancer prevention among chemically treated rats.[91] In Japanese women, regular consumption of *L. casei* and soy isoflavone since adolescence was significantly associated with decreased breast cancer risk.[92] So, long-term exposure was required to accomplish chemopreventive effect on cancer development. Therefore, it might open a new era in cancer treatment particularly using natural sources of probiotics along with some bacterial strains.

Immunomodulatory functions of probiotics

Probiotics played an influential role in modulating gastrointestinal health. Most of the reported mechanisms for this modulation were suppression of pathogenic bacteria by producing competitor environment.[93,94] Potential applications of probiotics are being expanded beyond alleviating gastrointestinal disorders to include benefits involving antihypertension, immunomodulation, improving serum lipid profiles, and alleviation of postmenopausal disorders. All the aforementioned benefits are explored in cell-based experiments and scientists are looking for *in-vivo* justifications.

Probiotic organisms are not only meant for immune systems encouragement but have many other useful properties. *Saccharomyces cerevisiae* Boulardii, (Biocodex) *Bifidobacterium animalis* Bb-12 (Chr. Hansen), *L. casei* Shirota (Yakult), *Bifidobacterium lactis* DR10, *Lactobacillus johnsonii* La1, *and Lactobacillus rhamnosus* GG (Valio, Culturelle) are known for their immunomodulatory characteristics.[34,95,96] Probiotics probably elevates immunologic barrier via inflammatory responses and enhancing intestinal immunoglobulin A (IgA).[94,97,98] Probiotics can enhance cellular, non-specific immune response by activation of macrophages, NK cells, antigen-specific cytotoxic T-lymphocytes, release of various cytokines in dosage dependent manner strain specific manner. Supplementation of probiotic organism at earlier ages could help to avoid immune-mediated illnesses. Probiotics also played pivotal role in pregnancy. They may have positive effects on fetal immunity particularly on transforming growth factor-β1 levels, cord blood IFN-γ levels and breast milk IgA. Yogurt or fermented milk may also deliver probiotics to improve mucosal immune system of the gut via cytokine-producing cells and enhancing number of IgA+ cells in effector wall of intestine.[38,96]

Inhibitory effects of probiotics

Probiotics can be used as natural cancer therapeutic agents due to little cytotoxic activity. Probiotics also produce specific growth inhibitors targeting no other than cancer cells.[99,100] Probiotic strains including *B. animalis, L. acidophilus, Bifidobacterium infantis, Lactobacillus paracasei, Bifidobacterium bifidum* were observed to reduce cancer cell growth in MCF7 cells.[101,102] *L. helveticus* R389 was involved in increased immunity booster; cytokines (including IL-10 and IL-4) and decreased growth of tumor cells when receive 4T1 mouse mammary adenocarcinoma cells injection subcutaneous to murine model (BALB/c).[77,102]

Enterococcus lactis IW5 produce metabolites having cytotoxic potential on various cancer cells. These metabolites after 24 h of incubation reduce the growth of breast cancer cells. These cytotoxic metabolites had antiproliferative effect positively different from *E. lactis* IW5 treated group as compared to the untreated control group. Antiproliferative properties of proteinaceous postbiotic metabolites (PPM) produced by *L. plantarum* I-UL4 on MFC7 cancerous cells were evaluated. Probiotic bacteria were grown on modified MRS (De Man, Rogosa and Sharpe agar) media supplemented with Tween 80 and the metabolites (PPM) produced were cytotoxic toward MFC7 cells in dosage and time-dependent manner. The greatest intoxicating antiproliferative effect showed by the lowest viable cell count was witnessed at 24 h of incubation. Moreover 80.87% of apoptotic MCF7 cells were observed at 48 h incubation. Results showed that the probiotic strain *L. plantarum* I-UL4 producing PPM significantly reduce the number of cancer cells, in the media supplemented with Tween 80.[103] Probiotic strains also showed antineoplastic activities inhibiting mammary tumor in animal models, emphasizing hypothetically universal effects of probiotics as anticarcinogenic agents.[104–107]

Prebiotics, synbiotics, and breast cancer

Prebiotics are low molecular weight carbohydrates (2–10 carbons) which are not easily digested, including certain resistant starches and fibers.[89] Widely describe prebiotics are nondigestible oligosaccharides, e.g., fructo-oligosaccharides. In the human intestine, they are poorly digested reaching unaltered to the colon acting as a substrate for the gut microflora. Number of Lactobacilli and Bifidobacteria were specifically stimulated by these prebiotics at the expense of another pathogenic microflora. Burns and Rowland extensively reviewed the anticarcinogenicity of probiotics and prebiotics.[108,109] Supplements containing probiotics and prebiotics had shielding effects against a wide range of procedures including induction of DNA damage in the colonic mucosa of rats.[89,110]

With probable anticancer properties, identifying probiotics, prebiotics, and synbiotics is expensive and time consuming, due to variety and number of these agents when working on animal models. *In-vitro* approaches are more practical alternative. The vital importance of DNA damage in the initiation and progression of cancer and reduction in genotoxicity by synbiotics is considered a highly applicable endpoint.[111] Another study suggested preventive role of prebiotics/dietary fibers in chemically induced mammary cancer using mouse model.[109]

Kassayova et al. worked on murine model providing them with a probiotic strain *L. plantarum* along with its associated prebiotic inulin while inducing mammary carcinogenesis to the animal by 7,12dimethylbena anthracene. Tumor frequency was significantly reduced using a combination of pro and prebiotics. Furthermore, it was observed that *L. plantarum* is very effective (via immunomodulatory mechanism) against breast cancer even in the absence of prebiotics.[77,109]

Conclusion

Probiotics have a vast range of beneficial properties and gained an increasing medical importance over the last decade. Probiotics enhance immune system and anti-inflammatory activities. Long-term consumption of probiotics was significantly associated with suppression of breast cancer formation and proliferation. Laboratory-based investigations including animal model and human breast cancer cells had shown antitumor effects of probiotics, but further studies involving humans in clinical trials are required to understand insight mechanisms and to use probiotics as cancer therapeutics. Probiotics are more cost effective and have less harmful effects as compared to various pharmacological applications like monoclonal antibodies. Therapeutic application of probiotics gained more interest for the role of gut microbiota in disease and health. Future success of probiotics depends upon continued explication of complex interactions between microbiota and host cells. In general, food containing probiotic producing microorganisms should be the part of routine diet to practice healthy life style.

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