

Probiotics: A Promising Anti-Cancer Agent



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Abstract

Even in today's modern era with sophisticated diagnostic and treatment facilities both infectious diseases and non-infectious disease are still a major threat to human health and well-being. The readily available probiotics have been under looked as an agent for improving human health and rendering immunity against these diseases. Probiotics are bacteria, molds and yeasts found in dairy products, plants, meat products, sewage, manure, humans and animals. Probiotic has the ability to improve health condition like gastrointestinal infections, genitourinary infections, allergies, urinary tract infections, certain bowel disorders, immune disorders, *Helicobacter pylori* infection and cancer etc. The bacterial components or metabolites of probiotics play an important role in prevention of variety of diseases. Cancer is one of the major threats to the human health. Through different mechanisms, probiotics in the form of single bacterial strain or a combination of many have shown anticancer activity in humans. Promising results are being obtained from recent research on anticancer activity of probiotics. Thus, the aim of this present review paper is to highlight the role of probiotic bacteria against cancer.

Keywords: Probiotic bacteria; Human health; Dairy products; Anti-carcinogen; Lactobacilli; Cancer; *Lactobacillus rhamnosus*; *Bifidobacterium longum*; *Bifidobacterium breve*; *Saccharomyces boulardii*; *Bifidobacterial*; Collaboration; B-Glucuronidase; *Lactobacillus acidophilus*; Azoreductase; *L. casei*; *L. Acidophilus*; Bacillus polyfermenticus; Gundruk; Sinki; Kimchi Taama

Abbreviations: WHO: World Health Organization; L: *Lactobacillus*; B: Bacillus; MAPK: Mitogen-Activated Protein Kinase; NK: Natural Killer cell

Introduction

Nobel Prize winner Élie Metchnikoff in early 20th century observed that people consuming fair amount of fermented milk products lived longer than average in Bulgaria. Lilly and Stillwell coined the word 'probiotics' in 1965 as growth promoting factor. The word probiotic refers to the mechanisms involved in selectively removing pathogens. According to World Health Organization (WHO), live microorganisms which when administered into host in sufficient amount will provide health benefits are called probiotics. From the time of early human civilization probiotics have always been used in one or another form. Currently, realizing the health benefits of probiotics pills, food, powders and infant formula containing beneficial microorganisms have been availed commercially. It has been proven that most of commercially available probiotics are safe and improve human health [1-4].

Microorganisms should have some basic properties to be considered as probiotic. Probiotics are non-pathogenic and nontoxic to the host. Their intake dose should be fairly large, and they should be viable. Likewise, they should have the

ability to survive in the acidic and basic environment of the stomach and duodenum respectively. Also, they should be able to stimulate the immune process within the body and should be able adhere to the gut epithelium and capable of exhibiting anti-cancerous activity. The following bacteria are being used as probiotics by different industries commercially in several countries. *Lactobacillus rhamnosus* GG in Finland, *Lactobacillus johnsonii* Lal in Switzerland, *Lactobacillus casei* Shirota in Japan, *Lactobacillus acidophilus* NCFM, *Saccharomyces boulardii* and *L. casei* CRL-43i Gilliland (La-Mo) in USA, *Lactobacillus plantarum* 299V in Sweden, *L. rhamnosus* 271 L. in France, *Lactobacillus delbruekii* sub species bulgaricus 2038 and *Streptococcus thermophilus* 1131, *Lactobacillus acidophilus* SBT-2062, *Bifidobacterium longum* SBT-2928 and *Bifidobacterium breve* in Japan. *Saccharomyces boulardii* yeast also show beneficial effect on human health [5,6].

It has been observed that colonic microflora produces many mutagens, tumor promoters and carcinogens utilizing dietary precursors and endogenously produced precursors [7].

Human faeces have shown mutagenic activities and also produce genotoxic substances of bacterial origin. Altering the gut microflora by the use of probiotics through dietary supplement will decrease the risk of colon cancer by interfering the carcinogenesis process. Increasing the numbers of lactobacilli and/or *bifidobacteria* in the colon by use of probiotics has shown to modify microflora of the colon. The natural products found in probiotics have drawn the attention of clinical nutritionists, scientists and industrialists to work in collaboration to utilize probiotics to develop drugs targeted against cancer which would show minimal or no side effects [7-10].

Anti-carcinogenic Effects of probiotics

There are several environmental, chemical pollutants, biological agents and genetic factors that subsequently lead to cancer. According to WHO, cancer is the second leading cause of death. Globally, 8.8 million deaths in 2015 were due to cancer. Among these deaths around 70% occur in low and middle-income countries. Probiotics are low cost, easily available, anti-pathogens and anti-cancerous microorganisms. The highly valuable probiotics can be availed locally by using traditionally fermented foods and this can improve human health and prevent cancer [11].

Various studies have revealed the processes by which probiotics exhibit anticancer activity. The ability of probiotics to act as anti-carcinogenic agent is supported by its ability to affect bacterial enzyme activity, to act as antigenotoxic agent both *in-vitro* and *in-vivo* [9]. Various strains of *Lactobacillus* and *Bifidobacterium*, their cellular components and metabolites have shown to decrease DNA damage in colon cells. *Bifidobacterium longum* and *Lactobacillus acidophilus* showed decreased activity of pro-carcinogenic enzyme and increased enzymatic activities of β -glucuronidase, nitroreductase and azoreductase [12-14]. Milk fermented with *L. acidophilus* La1 and enhance immune stimulation. Butyrate produce from probiotics acts on cancer cells by decreasing proliferation and increasing apoptosis [15,16].

Randomized trial conducted by Aso et al. [17] on patients who had their bladder tumor removed showed decreased recurrence of the tumor, 57% in subjects receiving *L. casei* compared to control subjects who had 83% recurrence [17,18]. Another *in-vitro* study showed that, probiotic strains of *L. acidophilus* LA102 and *L. casei* LC232 show anti-proliferative and cytotoxic activity against cell lines of colorectal cancer (Caco-2 and HRT-18). Among patients with colorectal cancer, increased number of T-helper cells and NK cells have been seen with *L. casei* which may have important role in suppressing tumor development. In East Asia, *Bacillus polyfermenticus* has been used for the management of gastrointestinal disorders. *In vitro* and *in-vivo* *B. polyfermenticus* showed that it suppresses cancer through the reduction of ErbB2 and ErbB3 and their downstream signaling molecules E2F-1 and cyclin D1[18-20].

In human, high expression of ErbB2 is responsible for bladder, breast, colon, and lung cancer. In addition, another study showed that *L. plantarum* can be a potential candidate for oral cancer therapy by increasing mRNA expression of Phosphatase and Tensin homolog (PTEN) and down regulation of mRNA expression and Mitogen-Activated Protein Kinases (MAPK). The probiotics mixture VSL#3 suppress the Cyclooxygenase-2 (COX-2) expression in Colo320 and SW480 intestinal epithelial cells. Anti-proliferative and pro-apoptotic activity of human-derived *Lactobacillus reuteri* ATCC PTA 6475 has also been studied. Promotion of apoptosis in *L. reuteri* is done by enhancing the activity of mitogen-activated protein kinase (MAPK) including c-Jun N-terminal kinase and p38 MAPK signaling cascade [21-24].

Conclusion

Globally, cancer is one of the major factors increasing morbidity and mortality. The cost of chemotherapy and its management also increases economic burden in the patients. Probiotics and their metabolites can be used as alternative remedies for the prevention of the cancer. Probiotic organisms show anti-cancerous activity by producing anti-tumorigenic compounds, reduce the effect of carcinogens by binding to them or reducing the absorption of mutagens through intestine and enhancing the immune system of the host. Majority of deaths due to cancer occur in lower and middle-income countries and the people either do not have quality testing and treatment facility or cannot afford costly treatment. It has been seen that traditionally used fermented foods have high concentration of probiotics. These foods can be prepared using low cost food items and have great health benefits. Fermented foods like gundruk, sinki, kimchi, taama, curd and many more have been used for centuries and they contain large number of probiotics. Thus, promoting the use of locally fermented foods can help reduce the risk of cancer remarkably.

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