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### Probiotics in cancer treatment

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#### ABSTRACT

Cancer is a broad term. It causes cells to divide uncontrollably. This can result in tumor damage to the immune system and other impairment that can be fatal. Some types of cancer cause rapid cell growth, while others cause cells to grow and divide at a slower rate. Certain forms of cancer result in visible growths called tumors. Probiotics are defined as live bacteria and yeasts that exert beneficial effects for health. In recent years various effects anti cancer properties have been highlighted. Probiotics and fermented milk products that have attracted the attention of scientists from various fields, such as health care, industry and pharmacy.

**Keywords:** Cancer, Probiotics, Lactobacillus, Bifidobacterium.

#### INTRODUCTION

Since 2012, cancer is classified as the second major death cause in different regions of the world with an estimated number of 14.1 million new cases and 8.2 million deaths and expected to increase up to 21 million cases with 13.2 million casualties by 2030. Cancer is caused by a progressive aggregation of mutations in the genetic material of cell. Uncontrolled proliferation of cells, insensibility of growth factors, and capacity to infect surrounding tissues are the general characteristic of malignant tumours observed in most cancer patient. Only 5-10% of all cancer cases can be attributed to genetic defects, while 90-95% of the cases are related to external factors. According to the World Cancer Report (2014), around one-third of all deaths caused by cancer are

resulting from high body mass, low fruits and vegetable intake, sedentary lifestyle, tobacco intake and alcohol ingestion [1].

Cancer cells have characteristics of genetic instabilities and accumulate somatic mutations rapidly [2-4]. There are various types of mutations such as point mutations, insertion/deletions, gene amplification and translocations in cancer cells. Some of them may lead to non synonymous somatic mutations altering the amino acid coding sequences and creating uncontrollable and abnormal proteins to promote cell proliferation [5]. Tumour-specific antigens (TSAs) called as neoantigens are created by genomic codon alterations, editing, usage, antigen processing and presentation [6, 7]. With the development of technologies of next generation sequencing (NGS),

it becomes apparent that human cancers are very complex, bearing thousands of mutations [8]. Lactic acid bacteria including the genus *Lactobacillus* and *Bifidobacterium* have been shown to exert beneficial effects in humans. Purified *Bifidobacterium* has cell wall anti tumor activities and induces activation of phagocytes to destroy growing tumor cells. Therefore resuming the equilibrium using the beneficial bacteria (called probiotics) for disease treatment and prevention has been regarded profitable [9].

Tumour microenvironment is constructed via the interactions between tumoral and non transformed cells. The latter have an active and often tumour-promoting role at all stages of tumorigenesis. The major non malignant cell types

that are detected in this environment are the cells of immune system, the tumour vasculature and lymphatic's, as well as the fibroblasts, pericytes and adipocytes [10]. The presence of a fraction of multipotent" cancer stem cells (CSC)" in solid tumours as well as haematological malignancies has resulted in suggestion of a new model for explanation of tumorigenesis process<sup>(11)</sup>. Probiotics have been shown to influence all cell types and pathways implicated in the metastasis [12]. Vaccine can induce antitumor immune response in humans with cancer [13]. A large number of antigens cause genetic damage and include neoplastic transformation of cells; these agents are termed as carcinogens. Carcinogens can be chemical, radiation/ionization, microbiological.

<b>INDICATION</b>	<b>PROBIOTIC STRAIN</b>
Traveller's diarrhoea	
Acute infectious diarrhoea in infants and children.	<i>Lactobacillus rhamnosus</i>
Antibiotic-associated Diarrhoea	
Atopic dermatitis	
Irritable bowel syndrome	<i>Bifidobacterium infantis</i>
Ulcerative colitis Crohn's Disease	<i>Escherichia coli nissle</i>

More than 80% of patients suffering from cancer use vitamin, minerals, herbs, and other supplements include probiotics during the course of their disease [14]. Most probiotics are safe. However, care should be taken when administering probiotics to severely ill or immune compromised patients. There have been rare incidents of sepsis, endocarditis and liver abscess during the use of *Lactobacillus*; additionally, fungemia has been reported with use of *S.boulardii*, primarily in patients with severe comorbidities [15, 16]. The most common side effects of probiotics are constipation, flatulence, hiccups, nausea, infection and rash [17]. Supplemental intake might change the metabolism of anticancer drugs and consequently affect the outcome of therapy. Moreover besides the beneficial effects associated with probiotic administration, there could be several adverse events, including potentially life-threatening conditions because of immunosuppression in cancer patients undergoing chemotherapy. As many as 50% or more of the patients with cancer take vitamins, herbal preparations and other supplements, including probiotics without medical guidance [18].

### **PROBIOTICS: CHRONIC DISEASE**

Probiotics, the beneficial bacteria commonly found in yogurt cultures, are popularly thought as an aid for good digestion. But scientists are discovering that probiotics and the resulting healthy balance of gut bacteria confer a broad spectrum of health benefits<sup>(19)</sup>. Evidence demonstrates that supplementing with the right mix of probiotic bacteria such as *Lactobacillus* and *Bifidobacterium* species can powerfully ward off many of the factors leading to chronic disease. Probiotics can restore your body's natural, intestine-based protection against a host of non-intestinal diseases and shield you from the diseases of aging [20]. Scientific studies have found associations between different species of *Lactobacillus* (*Lactobacillus acidophilus*, *Lactobacillus paracasei*, and *Lactobacillus rhamnosus*) and increased HDL cholesterol, balanced immune response and reduced markers of inflammation [21]. Similarly, associations have been found between *Bifido* bacterium species (*Bifidobacterium lactis*, *Bifidobacterium bifidum* and *Bifidobacterium longum*) and improved blood sugar control, decreased liver inflammation, and

reduced DNA damage that could trigger malignant cell development, respectively [22, 23].

Probiotics help your immune system at its best so it can detect and kill cells that can become cancer. Much of the probiotics research focuses on colon cancer, because most microorganisms live in our intestinal gut. Bacillus species exerts an anti cancer effect on human colon cancer cells stimulating Ig G production and modulates the number of CD4p, CD8p or Nk cells. In a recent study, daily consumption of probiotics for 6 months enhanced the clearance of human papillomavirus HPV which is known to be culprit of cervical cancer.

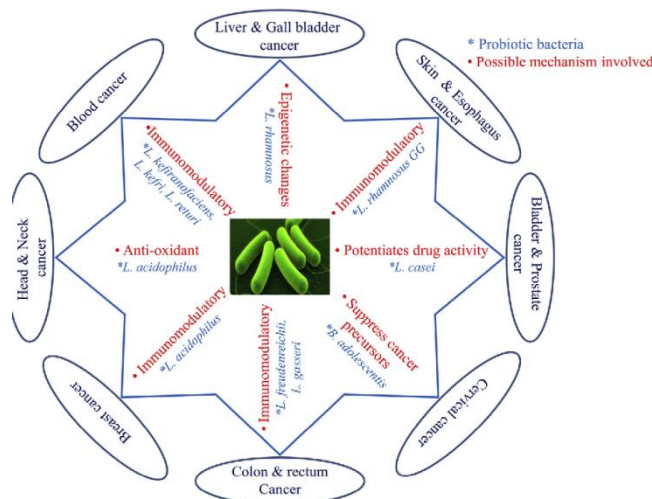
In recent years, reports have shown that dietary probiotics such as kefir have a great potential for cancer prevention and treatment. Kefir is fermented milk with Caucasian of Tibet origin, made from the incubation of kefir grains with raw milk or water. Kefir grains are a mixture of yeast and bacteria, living in a symbiotic association. Antibacterial, antifungal, anti-allergic and anti-inflammatory effects are some of the health beneficial properties of kefir grains. Furthermore, it is suggested that some of the bioactive compounds of kefir such as polysaccharides and peptides have great potential for inhibition of proliferation and induction of apoptosis in tumor cells. Many studies revealed that kefir acts on different cancers such as colorectal cancer, malignant T lymphocytes, Breast cancer and lung carcinoma.

Considerably, cell free supernants (CFS) from L.casei and L.rhamnosus have been shown to prevent colon cancer cell invasion suggesting that probiotics CFS has anti-metastatic bioactive substances that may participate in cell invasion decrease in vitro [24, 25]. Epithelial mesenchymal transition is a biological process that permits a polarized epithelial cell, which typically interacts with basement membrane through its basal surface, to undertake numerous biochemical alterations which result in acquisition of mesenchymal cell phenotype.

### The Powerful Role of Probiotics in Cancer [26-29]

Scientists have demonstrated that probiotics switch on protective signalling mechanisms that:

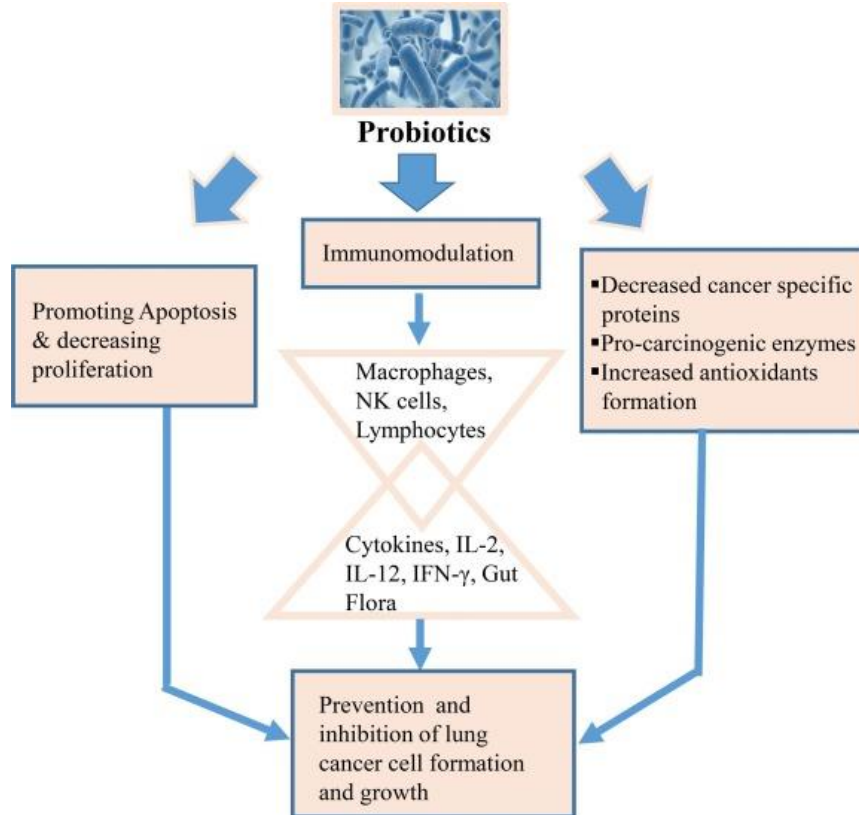
- Bind to potential carcinogens, promoting their excretion.
- Decrease enzymes implicated in the development of carcinogens.
- Suppress bacteria that convert pro-carcinogen molecules to carcinogens.
- Boost populations of immune cells that play an important role in tumour inhibition.
- Up-regulate immune cytokines to battle the early stage of cancer or other threats.
- Suppress the inflammatory response as the cancer or infection threat fades.



**Probiotics: Possible mechanism**

### Host factors that disrupt natural gut bacteria balance

- Antibiotics
- Infant formula
- Excessive hygiene
- Western diet
- Modern medical treatments
- Age



### Probiotics: action on different stages of cancer

Scientists Have Identified A Few Disease-Treatment Studies probiotic Species:

#### Lactobacillus acidophilus

- Reduced diarrhoea and improved bowel function in cases of radiation-induced enteritis.
- Increased HDL (good) cholesterol.
- Improved markers for metabolic syndrome, inflammation and heart disease.
- Improved allergy-driven immune response. Improved markers for ulcerative colitis and irritable bowel disease.
- Increased control of blood sugar [30]
- Decreased the DNA damage that can trigger malignant cell development [31].

#### Lactobacillus Rhamnosus

- Reduced diarrhoea and improved bowel discomfort in case of radiation-induced enteritis.
- Improved markers for metabolic syndrome, inflammation, and heart disease.
- Reduced allergic response to milk in milk sensitive patients.
- Improved markers for ulcerative colitis, and irritable bowel syndrome disease, including Crohn's disease.

#### Lactobacillus Paracasei

- Enhanced therapeutic management of minimal hepatic encephalopathy (MHE).
- Improved markers for metabolic syndrome, inflammation, and heart diseases in elderly patients.

- Improved markers for ulcerative colitis and irritable bowel disease.

### **Bifidobacterium lactis**

- Improved immune function in healthy, elderly individuals.
- Greater weight gain and less gut inflammation in preterm infants.
- Improved immune response and respiratory symptoms from birch pollen allergies in children.
- Increased control of blood sugar [32].

### **Bifidobacterium bifidum**

- Improved markers for liver inflammation and damage in alcohol-related liver disease.
- Improved inflammation profiles in ulcerative colitis and irritable bowel disease.

### **Bifidobacterium longum**

- Reduced diarrhoea and improved bowel function in cases of radiation-induced enteritis.
- Increased HDL (good) cholesterol.

- Improved markers for ulcerative colitis and irritable bowel disease including Chron's disease.
- Decreased the DNA damage that can trigger malignant cell development [33].

## **CONCLUSION**

Probiotics obtained increasing medical importance because of their beneficial effects on the host health. Oral administration of probiotics has multiple effects such as improvement of gastrointestinal barrier and inhibition of potential pathogens or carcinogens in the gut. Together with the enhancement of systemic immune or/and anti-inflammatory activities, probiotics plays an important part in reducing the risk of multiple chronic diseases including cancer. A traditional fermented milk product has been shown to inhibit in vitro proliferation of breast cancer cells but not normal mammary epithelial cells which implies that the bioactive substances prompt responses that are specifically detected in human cells [34]. Such phenotype change is accompanied by increased migratory capacity and invasiveness [35].

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