Al-Rafidain J Med Sci. 2023;4:52-59.
DOI: https://doi.org/10.54133/ajms.v4i.103

AJMS
Online ISSN (2789-3219)

Review Article

Role of Probiotics in the Prevention and Treatment of GIT Cancers: Updated Review

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Received: 11 February 2023; Revised: 28 March 2023; Accepted: 5 April 2023

Abstract
Cancer, one of the leading causes of death worldwide, has been the subject of extensive study by many researchers. Cancer is affected by both genetic and immune system factors in the human body. The gut microbiota plays an important role in the body's capacity to maintain homeostasis. Because of their beneficial effects on human health and their ability to successfully prevent and treat various chronic diseases, such as cancer, probiotics are becoming increasingly important in medicine. A wealth of research has shown that probiotic consumption can significantly helpful in cancer prevention and treatment. The goal of this review is to provide a thorough overview of the research on the function of probiotic bacteria in the prevention and treatment of gastrointestinal cancers.

Keywords: Probiotics, cancer, gastrointestinal tract, integrated therapy, immunomodulation.

دور البروبيوتيك في الوقاية من سرطانات الجهاز الهضمي وعلاجها: مراجعة محدثة

الخلاصة

السرطان، أحد الأسباب الرئيسية للوفاة في جميع أنحاء العالم، كان موضوع دراسة مستفيضة من قبل العديد من الباحثين. يتأثر السرطان بعوامل وراثية وجهازية في جسم الإنسان. تلعب ميكروبيوتا الأمعاء دورا مهما في قدرة الجسم على الحفاظ على التوازن. وبسبب آثارها المفيدة على صحة الإنسان وقدرتها على الوقاية بنجاح وعلاج الأمراض المزمنة المختلفة، مثل السرطان، أصبحت البروبيوتيك ذات أهمية متزايدة في الطب. أظهرت ثروة من الأبحاث أن استهلاك البروبيوتيك يمكن أن يساعد بشكل كبير في الوقاية من السرطان وعلاجه. الهدف من هذه المراجعة هو تقديم نظرة عامة شاملة على البحث حول وظيفة بكتيريا البروبيوتيك في الوقاية من سرطانات الجهاز الهضمي وعلاجها.

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Article Citation: Hassan DS, Hasary HJ, Hassan ZS. Role of probiotics in the prevention and treatment of GIT cancers: Updated review. *Al-Rafidain J Med Sci*. 2023;4:52-59. doi: 10.54133/ajms.v4i.103

INTRODUCTION

Cancer is one of the leading causes of death in the globe [1]. Despite recent attention paid to tumor treatment strategies, the number of people diagnosed with neoplastic syndromes continues to increase. As a result, researchers are trying to address this process by seeking novel treatments and preventative measures [2]. Although genetic factors undoubtedly influence cancer development, the organism's immunological state also has a substantial effect on it. This condition is closely associated with probiotic bacteria and commensal bacterial flora, which are mainly found in the gastrointestinal tract [2]. Gastrointestinal tract-related cancers account for 25% of all cancers identified globally, and gastrointestinal (GI) malignancies account for 9% of cancer-related fatalities [3]. They can be categorized into 3 types.

Gastric cancer

Gastric cancer (GC) kills 738,000 individuals each year, making it the world's second leading cause of death. It is also the world's fourth most prevalent cancer in general. At an advanced level, symptoms of the disease begin to show. Both environmental factors and specific genetic abnormalities add to the disease's development [4]. Although global patterns

in gastric cancer are improving, prevention should remain a top priority. The primary preventative measures are a healthy diet, H. pylori treatments, chemoprevention, and early detection testing. Dietary factors have a substantial impact on the development of stomach cancer [5]. Sporadic gastric cancer, early-onset gastric cancer, gastric stump cancer, and hereditary diffuse gastric cancer are the four types of stomach cancer (HDGC).

Colorectal cancer (CRC)

Colorectal cancer (CRC) is the third most common disease and the fourth leading cause of cancer-related death. The majority of CRC cases are discovered in Western countries, and its prevalence is increasing year after year. Colorectal cancer affects approximately 4%-5% of the population, and risk factors for CRC include age, a history of chronic illnesses, and way of life. The gut microbiota is significant in this context because dysbiosis can lead to colonic carcinogenesis through a chronic inflammatory process. *Fusobacterium* spp., *Bacteroides fragilis*, and enteropathogenic *Escherichia coli* are among the organisms in control of these multiphase pathways [6]. Mutations in oncogenes, DNA repair-related genes, and cancer suppressor genes contribute to the formation of CRC. Colorectal cancers are classified into three types based on the origin of the mutation: familial (25%), inherited (5%), and spontaneous (70%). This condition is caused by three kinds of pathogenic processes: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP) [7].

Other GIT cancers

Hepatocellular carcinoma is the most common type of liver cancer, originating from hepatocytes and accounting for more than 80% of all cases. It is produced by the interaction of environmental and genetic factors. Cirrhosis of the liver, infection with the hepatitis B and C viruses, excessive alcohol consumption, consumption of aflatoxin B1, and nonalcoholic steatohepatitis (NASH) are the major risk factors for the development of HCC [8]. Pancreatic cancer is another GIT cancer that is the seventh leading cause of cancer mortality and the fourteenth most common cancer globally [9]. It is clear that the quality of life is deteriorating as a result of cancer development and treatment protocols. Various studies are currently being conducted to evaluate the positive effects of probiotics on certain kinds of cancer, especially gastrointestinal tract cancers such as colorectal cancer, in order to improve the disease's treatment process [10]. Numerous in vivo and in vitro studies are being conducted to determine the efficacy of probiotics in cancer prevention and treatment. The word "probiotic," derived from the Greek phrase "for life," refers to a type of living bacteria that does not cause illness or harm to its hosts [11]. FAO/WHO defines probiotics as "live microorganisms that provide health benefits to the host when administered in sufficient amounts" [12]. The following points summarize and are illustrated in Figure 1, represent the major characteristics of probiotics, including non-pathogenic microorganism [2], capable to survive throughout the gastrointestinal tract [2], capable to endure bile salts [13], replicate in the intestinal medium [14], maintain a mutualistic relationship with the host [15], have positive immunomodulatory impacts [2], genetically not harmful [16], and produce safe metabolites like organic acids, bacteriocins, and hydrogen peroxide [17].

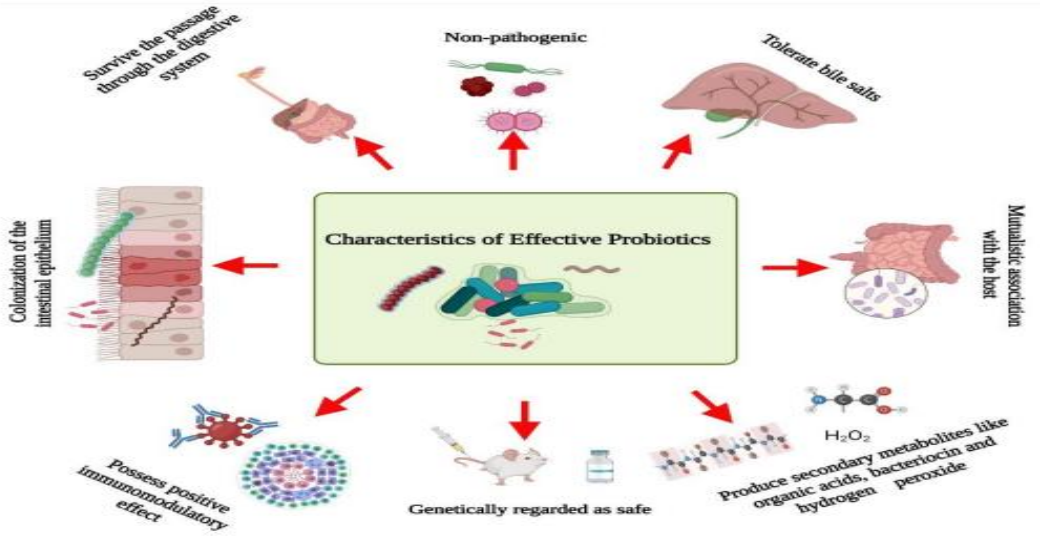

Figure 1: Schematic illustration of effectiveness features of probiotics [2].

Probiotics and Cancer

Goldin and Gorbach were the first to establish a connection between eating a high-lactobacillus diet and a lower risk of colon cancer. Their trial had a 40% success rate compared to the control group's 77% success rate [18]. Probiotics have recently received a lot of attention for their ability to modulate the growth and apoptosis processes of cancer cells, which has been studied both in vitro and in vivo. As a result of these advantageous properties, novel treatments could substantially substitute for invasive cancer therapies such as chemotherapy or radiotherapy [18]. The precise method by which probiotics work as an antitumor agent is unknown. Intestinal flora is engaged in a variety of metabolic processes and pathways that are required for such processes. Probiotic organisms, in general, play an important part in the preservation of homeostasis by protecting regular physicochemical conditions in the colon [19]. Furthermore, intestinal microflora may be involved in the control of GIT pH and bile salt form; for example, B. bifdum and L. acidophilus have been shown to be important in cancer prevention [20]. Furthermore, some probiotic strains regulate the quantity of other native species of gut flora while also balancing their metabolic processes [21]. Probiotics' anticancer effects can be described in a variety of ways [18,22], including changes in the composition and function of the gut microbiota, regulation of the intestinal flora's metabolic process, and synthesis of anticancer substances such as conjugated linoleic acid and short-chain fatty acids. They also include the prevention of cell proliferation and the enhancement of cancer cell apoptosis, influence on various carcinogenic and mutagenic factors, deactivation of carcinogenic materials introduced into the GI lumen (xenobiotics), immune system regulation, intestinal barrier enhancement, colonization resistance, and involvement in vitamin K and vitamin B production. As previously stated, different preliminary experiments performed by Goldin and Gorbach at the end of the 1970s and the results of their studies demonstrated that the administration of fermented milk products to the investigated rats increased the number of *L. acidophilus*, resulting in a decrease in destructive enzymes and putrefactive bacteria [18]. Furthermore, several studies on both people and rodents demonstrated the beneficial effects of probiotic strains on bacterial enzymes involved in tumor genesis. The food industry generally suggests a minimum level of 106 CFU/mL, and the FDA confirms that the daily human requirement for probiotics is 108-109 CFU/mL. Furthermore, regular intake of food probiotics is advised, and 100 g/day of food containing microflora should be consumed to release approximately 109 living cells into the intestines [22].

The Relationship of Probiotics with GIT Cancers

The definition of GI cancers is a multifactorial disease associated with complex processes such as immunity, genetics, environmental factors, dietary factors, and vital changes, all of which have a direct impact on the intestinal flora. Various studies have been conducted to investigate the beneficial effects of probiotics on GI cancers, and a number of important studies have proven the antiproliferative or pro-apoptotic effects of probiotics [23]. Gastric and colon cancers are the most common digestive system malignancies. Lactic acid bacteria and *Bifidobacterium speciosum* are the most common probiotics that have been studied for their impact on cancer cells. Various studies, however, involve *Escherichia coli*, *Enterococcus*, *Saccharomyces boulardii*, and *Streptococcus thermophiles* [23,24]. Recent study has found that the L. rhamnosus GG strain has anti-proliferative activity in patients with colon cancer and stomach carcinoma [24,25]. Another research found that *Bifidobacterium adolescentis* SPM0212 inhibited the proliferation of colon carcinoma cell lines HT29, SW 480, and Caco-2. Furthermore, several probiotic species, including *L. acidophilus* 606, *Bacillus polyfermenticus*, LGG/*Bifidobacterium animalis* subsp. *Lactis*, and LGG/Bb12, have been shown to induce apoptosis in human colon cancer cells [24]. Several studies in colorectal cancers have shown that consuming probiotics is an effective strategy for keeping a healthy intestinal flora and lowering the incidence of colon cancer [25]. Several in vitro and in vivo studies on this topic have been carried out using animal models and human cancer cell lines. In randomized, placebo-controlled trials, probiotics were shown to prevent and slow the growth of intestinal cancer. (RCTs). Probiotics can have intraluminal, systemic, and direct effects on the gastrointestinal mucosa [26]. Intraluminal impacts include altered gut microbiota enzyme activity, increased short-chain fatty acid production, competitive eradication of pathogenic intestinal flora, attachment to carcinogens and mutagens, and decreased carcinogenic secondary bile acids [24]. The results are unequivocally in favor of probiotics' diverse immunomodulatory role in colorectal cancer (CRC), particularly their ability to control gut inflammation, which has been identified as a major causal factor in CRC in a randomized controlled study [27,28]. Probiotics may be useful in this area not only by preventing CRC but also by reducing the negative effects of colorectal surgery and CRC treatment [22]. Experiments that developed the administration of probiotics for the inhibition of mucositis in patients with CRC cancer yielded positive results. The use of probiotics for CRC protection is dependent on the organism. Several studies found that giving eight different probiotic strains containing *L. rhamnosus* GG to CRC patients getting chemotherapy and radiotherapy reduced the occurrence of diarrhea significantly [27]. It is the fourth most common cancer in men and the seventh most common cancer in women in gastric cancers, which are the fourth

most common cancer type globally and the third leading cause of death from the disease [29]. In 2020, there will be over 1 million additional cases of stomach cancer [30], with surgical intervention being the first line of defense. Enteral nutrition (EN) could have a substantial impact on patients' recovery from gastric cancer during the postoperative period. Enteral nutrition, on the other hand, can result in a variety of complications, the most prevalent of which is diarrhea, which causes electrolyte and fluid loss. The use of probiotics can reduce the frequency of diarrhea. Patients with GC who were given a combination of EN and probiotics in the postoperative period showed promising results, such as an improvement in the immune system and a decrease in the inflammatory response. Zhao *et al*. performed a randomized controlled trial (RCT) to support the use of probiotics in the treatment of EN complications [31]. The majority of research on the relationship between probiotics and GC are focused on combating *Helicobacter pylori* (H. pylori) infection, which has the ability to disrupt the function of the acid mucus barrier and colonize the stomach epithelium. Probiotics such as *Bifidum*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius*, and others have been shown in animal models to have beneficial inhibitory effects on *H. pylori* infection [32]. Despite the fact that most studies on the function of probiotics in cancer have been conducted on CRC and GC, other types of digestive cancer, such as liver, pancreatic, and esophageal cancer, have also been conducted [25]. Previous research indicates that probiotics reduce the risk of pancreatic cancer via a variety of mechanisms, including the management of risk factors such as obesity, inflammation, pancreatic necrosis, and diabetes [33]. Few studies have been conducted on the effects of probiotics on liver cancer. Studies have shown that probiotics reduce liver damage, proinflammatory cytokines, and inflammation while boosting antioxidant activity. As a result, probiotics can be concluded to serve an important role in the prevention of liver cancer [22]. As a consequence, probiotics may be able to alter gut flora consistency and reduce the size of liver tumors. In addition, probiotic administration was investigated in the research to regulate angiogenic factors [34].

METHODS

The current review was designed specifically to concentrate on the primary benefits of probiotic consumption and its role in cancer therapy. This review was created by searching Google Scholar, PubMed, and the Research Gate database for published scientific papers acquired from rigorous scientific experiments between 2010 and 2023. Keywords included "probiotics," "cancer," "gastrointestinal tract," "integrated therapy," "immunomodulation," "cancer prevention," and "impact of probiotics on cancer occurrence."

Inclusion and exclusion criteria

Books, original studies, clinical trials, websites, case reports, and review articles focusing on the positive effects of gut microbiota in cancer prevention, various strains of intestinal flora and their effects on immunomodulation, and the role of GI flora during cancer management are included as inclusion criteria. Exclusion criteria included all articles pertaining to probiotics and breast cancer, probiotics and leukemia, probiotic manufacturing, and probiotic isolation and identification.

DISCUSSION

The human gastrointestinal tract is home to a diverse and active community of organisms known as gut flora, which are primarily represented by different bacterial strains. This has a significant effect on the host, both during homeostasis and during sickness [35]. The presence of so many gut bacteria suggests that the human body contains approximately ten times as many prokaryotic cells as eukaryotic cells [36]. Spirochaetes, Bacteroides, Firmicutes, Actinobacteria, Sinicobacteria, Proteobacteria, and Fusobacteria are among the bacteria phyla found in human gut [2]. Bacteroidetes (Bacillus spp., Lactobacillus spp., and Clostridium spp.) and intestinal Firmicutes (Bacillus spp., Lactobacillus spp., and Clostridium spp.) make for 90% of the total number of bacteria present [2,37]. During the first three years of human life, the microbiota in the digestive system changes and matures [36]. The proper bacterial population balance maintains the gastrointestinal tract's homeostasis. The gut microbiota, on the other hand, is constantly changing. As a consequence, a variety of factors such as inadequate nutrition, medication, stress, digestive tract diseases, and obesity can all add to intestinal homeostasis disorders. Proinflammatory immune responses may arise as a result of digestive system instability, triggering disease processes. (cancer, for instance). The imbalance of the intestinal medium could be attributed to the formation of tumors in the GIT and other locations throughout the body [18,38]. Probiotics are defined as live organisms that, when consumed in sufficient quantities, add to human health [2,39]. Probiotics are mostly found in cultured milk products like yogurt and kefir, as well as silage like cabbage and cucumbers. The most prevalent genera of organisms implicated in human diets are Lactobacillus, Enterococcus, Bifidobacterium, Streptococcus, and Lactococcus, though some Saccharomyces and Bacillus strains could also be used [40]. The main advantage of probiotics is their effect on the evolution of the intestinal flora, which prevents microorganisms and promotes proper balance between macrobiotics (necessary for normal flora function) and pathogens. The primary beneficial effects of probiotics are the restoration and maintenance of intestinal equilibrium following any

disturbance event. Furthermore, according to a number of in vitro investigations [18], probiotics may be important in the regulation of cancer cell growth and death. *Lactobacillus rhamnosus* GG strain, for example, has been shown to inhibit proliferation and cause apoptosis in HGC-27 mouse colon cancer cells and Caco-2, DLD-1, and HT-29 human colon cancer cells [24,41-43]. Probiotics and their metabolites, such as butyrate and pyridoxine, have been studied as possible anticancer treatments in preclinical studies [44]. Butyric acid aids in the control of colon cell division, proliferation, and apoptosis. Colon cell metabolism produces approximately 70%-90% of butyrate, and colorectal cancer patients have significantly less of this acid in their stool than healthy people [44]. Short-chain fatty acids (SCFAs) found in probiotics fuel colon cells while also preserving the intestine's acidic environment, preventing the formation of excess secondary bile acids, and promoting acidosis and apoptosis in cancerous cells [45]. SCFAs have the ability to modulate both the systemic immune response and local gut defense. SCFAs, which maintain intestinal barrier function, cause tight junction expression and antimicrobial peptide production in intestinal epithelial cells. Figure 2 shows how SCFAs act to reduce inflammation by interfering with intestinal G protein-coupled receptors and regulating the immune system.

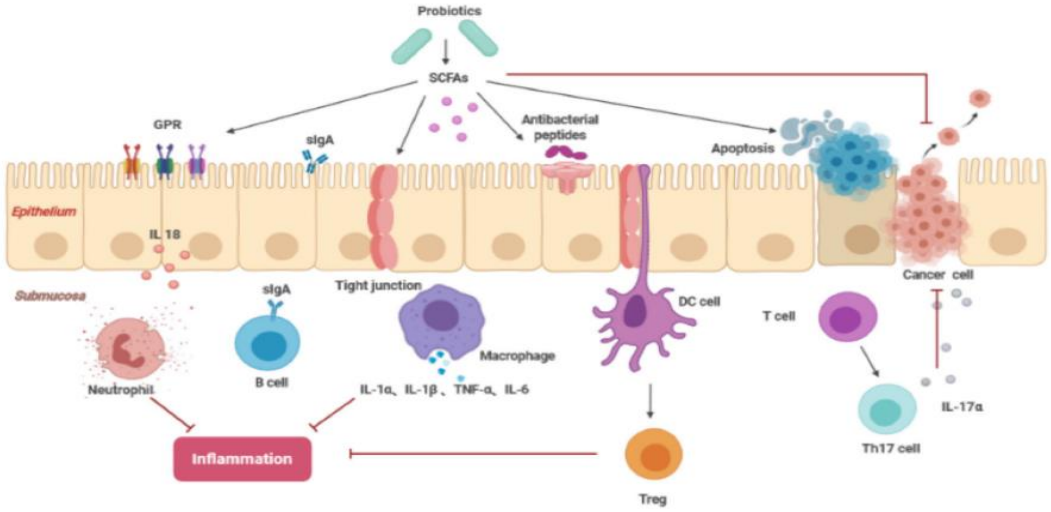

Figure 2: The role of short-chain fatty acids (SCFAs) in preventing cancer (sIgA, soluble IgA, GPR, G protein coupled free fatty acid receptor, DC cell, regulatory T cell, Th17, T helper cell 17) [44].

As previously stated, linoleic acid (LA) and its isomer, conjugated linoleic acid (CLA), both increase the expression of apoptosis genes such as Bcl-2, caspase 3, and caspase 9, which inhibit the proliferation of colon cancer cells [18]. Atypical gut flora consistency is linked to an increased chance of colorectal cancer. The number of bacteria that can cause gastrointestinal inflammatory illnesses, toxins, and carcinogenic compounds is often greater in colorectal cancer patients' intestinal microflora [46]. Chronic inflammatory states may increase the risk of cancer [47]. Clostridium spp. were found in direct interaction with colon cells beneath the mucus layer, penetrating the submucosa and causing long-term local inflammation [48]. Furthermore, elevated Clostridium spp., a gene and protein profile linked with inflammation, was discovered in colorectal cancer tissues. All of these factors led to tumor development and spread [47]. Chandel *et al.* discovered that combining *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, or both with celecoxib reduced NF-kB, COX-2, b-catenin, and K-ras carcinogenic indicators in a colon cancer animal model [19]. Another preclinical study discovered that altering intestinal bacteria with *Bifidobacterium bifidum* and *Lactobacillus acidophilus* could be used as successful biotherapeutic agents for colon cancer prevention [49]. In addition to gastrointestinal cancers, abnormal changes in the composition and function of intestinal bacteria may have an effect on non-gastrointestinal tumors such as pancreatic cancer, liver cancer, and even breast cancer [50,51]. According to studies, the anticancer effects of probiotics are primarily due to changes in intestinal flora, changes in metabolic activity, binding and degradation of carcinogenic substances, immunomodulation to reduce chronic inflammation, a decrease in intestinal pH, and the prevention of enzymes that could potentially produce carcinogenic substances, as shown in Figure 3 [47,48]. Probiotic clinical trials have become much more prevalent in recent years, with over 100 being registered each year since 2010. Probiotics are presently being studied in the United States, Europe, and Asia to see how they can improve oral health, gut microorganisms, immune balancing, pH maintenance, and antimicrobial and anticancer activity [2]. The most commonly registered probiotic

strains were *L. rhamnosus* GG and *Bifidobacterium animalis* [52]. Furthermore, there have been more research on children than on the elderly [52]. Furthermore, study has shown that probiotic strains are effective in reducing the negative effects of cancer-related microbiota dysbiosis and are effective in the treatment of malignancies, as shown in Table 1 [53]. As a result, in at-risk groups, probiotics may be used as an alternative biological therapy to cure or possibly prevent colorectal cancer [49].

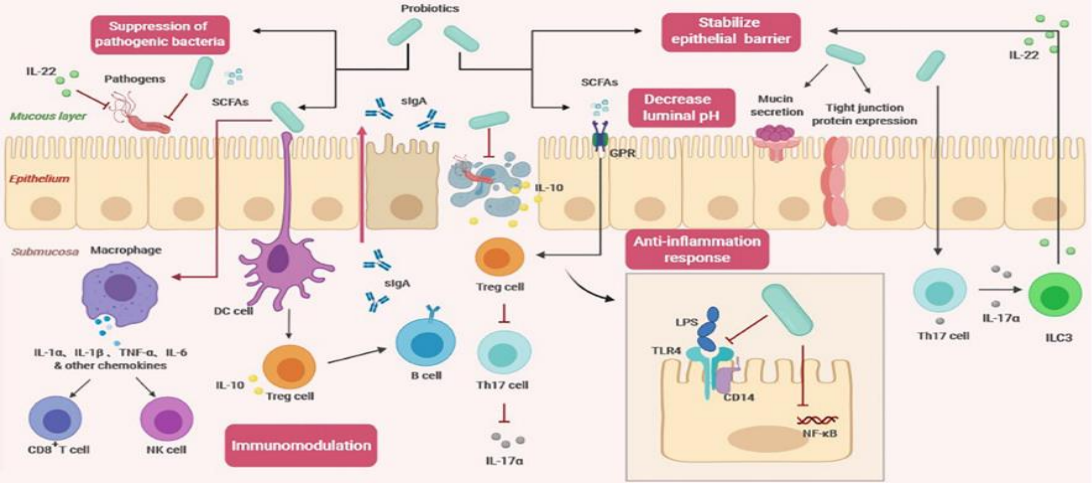

Figure 3: The impacts of probiotics on the host (DC cell, dendritic cell; SCFAs, short-chain fatty acids; GPR, G protein coupled free fatty acid receptor; sIgA, soluble IgA; Treg cell, regulatory T cell; Th17, T helper cell 17; NK cell, Natural killer cell; ILC3, Type 3 innate lymphocyte; NF-kb, nuclear factor-kB; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4.) [44].

Table 1: Outcomes of the conducted clinical experiments implying various probiotics specious in the cancer prophylaxis and management.

Organism strain	Subject	Duration of Therapy	Outcome	Reference
Streptococcus thermophilus and *Lactobacillus delbruckii* subsp. *Bulgaricus*	45,241 healthy participants 14,178 men and 31063 women	12 years	Yogurt consumption increased, especially among men, and was correlated with a decrease in the incidence of colon cancer.	Pala *et al*., [54]
Lactobacillus gasseri OLL2716 (LG21)	10 participants with colorectal cancer and 20 healthy subjects	12 weeks	Increase the quantity of Lactobacillus-related organisms. Increase isobutyric acid synthesis, NK cell activity, and the prevalence of *Clostridium perfringens*	Ohara *et al*., 2010 [21]
Lactobacillus rhamnosus LC705, *Propionibacterium freudenreichii* ssp. *shermanii* JS	38 men (24-55 years old)	4 weeks	Reduced activity of urease and β-glucosidase, increase the *Propionibacterium* and *Lactobacillus* bacterial growth.	Śliżewska *et al*., 2022 [18]
Lactobacillus rhamnosus LC705, *Propionibacterium freudenreichii* subsp. *shermanii*	90 male participants with high aflatoxin levels in urine.	5 weeks	AFB-N7-guanine (aflatoxin B1) urine excretion decreased as a result of a 61.5% drop in a liver cancer biomarker.	Śliżewska *et al*., 2022 [18]
Lactobacillus acidophilus, *Lactobacillus plantarum*, *Bifidobacterium lactis*, and *Saccharomyces boulardi*.	164 cases with colorectal cancer undergoing colorectal surgery.	30 days	Lessen post-surgical problems. Expression of SOCS3 gene, TNF gene, and the level of circulating IL-6 were all positively correlated in the probiotic group.	Aisu *et al*., 2015 [28]
Lactobacillus plantarum CGMCC, *Lactobacillus acidophilus*-11, *Bifidobacterium longum*-88.	150 known cases with colorectal carcinoma.	6 days before surgery and 10 days after.	Decreased duration of antibiotic therapy, decreased serum zonulin levels, shorten the duration of post-operative pyrexia, and decreased the frequency of post-operative infection, and p38 MAPK signaling inhibition.	Liu *et al*., 2013 [55]
Bifidobacterium longum	60 cases with colorectal cancer undergoing colon resection	3 days	Increased growth of *Bifidobacterium*, reduced growth of *Escherichia coli*.	Zhang *et al*., 2012 [56]
Bifidobacterium breve Yakult.	42 patients during chemotherapy	6 weeks	Lowered incidence of fever, fewer IV antibiotics were required than the control group.	Wada *et al*., 2010 [57]

Conclusion

Cancer has been documented as a significant health problem since antiquity, and its prevalence is still increasing today. Cancer, a disease defined by uncontrolled cell proliferation, kills millions of people each year and is considered one of humanity's most severe health problems. As a consequence, many scientists are presently working to develop a variety of cancer treatment methods. Because of their positive effects on the human body, which correlate with disease prevention and treatment in the absence of side effects, probiotics have increased in medical significance. According to the powerful mechanisms of action outlined in this paper, probiotic organisms can have localized, promising effects on the complete body. Some probiotic species have been shown to inhibit the growth of cancer cells in the gastrointestinal system. Finally, numerous studies have found that probiotics can play an important part in cancer prevention and treatment.

Conflict of interests

The authors declared no conflict of interests.

Source of fund

No specific fund received.

Data sharing statement

N/A

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