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INVESTIGATION ON THE EFFECTIVENESS OF PROBIOTIC MICROBIOTA ON CANCER

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Authors PK, NP and KMN desigmed the study and carried out literature survey and draft the manuscript. Authors JAPR and MLMDKA carried out the corrections. All authors read and approved the final manuscript.

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Review Article

ABSTRACT

Cancer is the one of the deadly menace diseases with high medical significance which remains one of the keys that causes ailments and death, the security and firmness of the typical chemotherapeutics drugs and artificial agents used to accomplish cancer are doubtful now a days. These mediators affect the quality of life or sometimes they causative for progress of drug resistance and are not judicious to the majority of the patients So the clinical management of the cancer with high efficiency can done with the probiotic microbiota. An imbalance in the gut microbiota promotes the progress of carcinogenesis through several mechanisms, including inflammation, initiation of carcinogens, and tumorigenic pathways as well. In vivo and molecular studies have exhibited the support to role of probiotics in cancer. Probiotic agents are live microbes or components of microbes that have a positive effect on the host. They exert their action through interaction with the immune system of the host. Some of this effect is localized and some is in improvement in total body system. The Probiotic bacteria are the live microorganisms that, when directed in acceptable amounts, deliberate a healthy benefit on the host, and they have been considered for their protective anti-tumour effects. This review emphases on the role of probiotic microbiota as substitute for the prevention and treatment of cancer in the relation between gut microbiota and the progress of cancer.

Keywords: Cancer; probiotics; immune system; immunobiotics; health benefits.

1. INTRODUCTION

Cancer is a serious danger to human life and health. Traditional cancer treatment methods, such as radiotherapy and chemotherapy, result in low endurance rates or severe side effects on normal cells, which limits the therapeutic effect due to the development of drug resistance and lack of tumor specific drugs [1]. Some of the main types of cancer that cause substantial mortality are colorectal, prostate, lung, stomach, liver and breast cancers [2]. The occurrence of this disease is currently very high and the number of cases lingers to rise. Global numbers show that in women colon cancer is second to breast cancer and in men, it is third base after lung and prostate cancer [3]. There are three types

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of inhibition: primary, secondary, and late [4]. GI bacteria also play a critical role in the development of homeostasis of the innate and adaptive immune system, and an modification of its composition contributes to various diseases including metabolic syndromes 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 [5]. Probiotics are beneficial bacteria that help sustain the homeostasis of gut microenvironment [6]. To avert and treat various types of cancer effectively, probiotics play an important role. This is addressed in several studies [7]. The probiotics recommended for human applications are primarily the two classes of lactic-acid-producing microorganisms, the *bifidobacteria* (e.g, *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium adolescentis*) and the low-GC-content lactic acid bacteria such as *Enterococcus* spp, *Lactobacillus* spp, *Lactococcus* spp, *Leuconostoc* spp, *Pediococcus* spp, and *Streptococcus* spp. [8]. Probiotics are valuable bacteria that help sustain the homeostasis of gut microenvironment [6]. Food plays an important role in the etiology of cancer. Nutritional support, in addressing the specific needs of this group of patients, is required to help improve prognosis and decrease the consequences of cancer-associated nutritional deficiency. Effective therapy improves patient's eminence of life and also is survival. Early intervention with nutritious supplementation has been shown to halt malnutrition and may recover outcome in some patients. That increased nutritional intake insufficient to stop the development of cachexia, reflecting the intricate pathogenesis of this condition. Some dietary factors, for instance probiotics, have a role in establishing a healthy bowel, including the risk for developing cancer. *Lactobacillus acidophilus*, *Lactobacillus casei* Shirota strain, and *Lactobacillus* GG have been shown to have repressive properties on chemically induced tumours in animals [9, 10]. The concept of probiotics grew from a theory first proposed by Metchnikoff who suggested that the long, healthy life of Bulgarian peasants could be accredited to their consumption of fermented milk products. A diversity of health benefits have been associated with LAB such as enhancement of lactose intolerance, regulation of gastrointestinal stasis, resistance to communicable digestive diseases, particularly rotavirus-associated diarrhoea in infants, and immunomodulation [11]. They are the live microbial food ingredient that is valuable to health. A probiotic organism must be non-pathogenic and non-toxic, and also resistant to low pH and to bile salts to improve its chances of endurance in the gastrointestinal tract [12]. Probiotics have ability to modify the inflammatory factors and enhance immune status inspired researchers to term this exact probiotic genus including the lactic acid probiotics as "immunobiotics" [13]. The part of probiotics and natural bioactive compounds in modulation of the common molecular pathways in pathogenesis of atherosclerosis and cancer: cancer contribute in more than 60% of death rate in highly-developed economic countries. Within the frame of referenced components, probiotics, prebiotics, plants and their extracts and poly-unsaturated fatty acids (PUFA) could be efficiently used to reduction chronic disease risk [14]. Greatest probiotics are members of two genera of lactic acid producing bacteria (LAB), *Lactobacillus* and *Bifidobacterium, but Saccharomyces* and *Enterococcus* are also used. Many of the bacteria used for probiotic preparations have been isolated from human faecal samples to maximise the likelihood of compatibility with the human gut microflora and hence improve their chances of existence [11]. As the cancer treatment method such as the chemotherapy radiotherapy have more lateral effects, we can use probiotic microbiota for the inhibition and curing of cancer which we are going to focus in this review.

1.1 Probiotics

Probiotics are the microbe or a group of microbes that resides within the gut and nurtures the host body inside [15]. They are commonly taken as preparations with live cultures which contain bacteria, such as *lactobacilli, lactococci or bifidobacteria* that has been isolated from environments [16]. The miscellaneous characteristics of probiotics have been familiar as health promoters, examiners in current year has mainly focused on inspecting the culture conditions and viability of probiotic strains during processing and storage; sensitivity to low pH values, gastric fluid, bile, pancreatic and intestinal juices and intestinal or respiratory mucus; adherence to isolated cells or cell cultures and interactions with other (pathogenic) microorganisms.

1.2 Postbiotics

The bacterial products, in the absenteeism of viable organisms, may have like effects on signaling pathways and barrier function. The bacterial products are sketchily considered as postbiotics and can be defined as non-viable bacterial products or metabolic by products from probiotic microorganisms that have biotic activity in the host [17]. Over-all, postbiotics embrace bacterial metabolic by products, such as bacteriocins, organic acids, ethanol, diacetyl, acetaldehydes and hydrogen peroxide, but it is also found that certain heat-killed probiotics can

also hold significant bacterial structures that may exert biotic activity in the host (Islam, 2013). Research shows that these metabolic products have a wide repressive property toward pathogenic microbes and, therefore, can be used as an alternate to antibiotics [18]. Postbiotics are non-toxic, non-pathogenic and resistance to hydrolysis by mammalian enzymes, as these are non-viable infectious products or metabolic byproducts from probiotics. In some instances, post biotics can also improve barrier function against species like *Saccharomyces boulardii*, and improve angiogenesis *in vitro* and *in vivo* in epithelial cells by initiation of a2b1 integrin collagen receptors [19]. Similar properties have also been identified in several other probiotic species of *Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium infantis, Bacteroides fragilis, Lactobacillus, Escherichia coli* and *Faecalibacterium prausnitzi*i [20].

1.3 Prebiotics

Additional exploration of probiotics has led to the advance of prebiotics, which are certain nutrients that alter the gut microbial flora even though not easily digested by humans but have a selective role in incentive of growth or activity of helpful bacterial species in the gut [21] Some of the usually known prebiotics includes bifidogenic properties of insulin, oligofructose, and fructo-oligosaccharides (FOS) synthetically formed from sucrose, as well as galactose- containing and xylose-containing oligosaccharides [22]. The fermentation of carbohydrates represents a chief source of energy for epithelial cells in the colon and prebiotics can willingly fulfill these requirements as a result of their fermentation by gut microbiota, such as bifidobacteria. Besides bifidobacteria, there are numerous other gut microorganisms that play a noteworthy role in fermenting these non-digestible oligosaccharides. Some of the examples of the prebiotics, laterally with their natural sources and Prebiotics can be gained naturally from sources like vegetables, fruits, and grains consumed in our daily life. Prebiotics not only serve as an energy source but also have numerous health benefits such as reducing the prevalence and duration of diarrhea, providing relief from inflammation and other symptoms associated with intestinal bowel disorders, and exerting protective effects to prevent colon cancer [23]. Prebiotics are also concerned in enhancing the bioavailability and uptake of minerals, dropping of some risk factors for cardiovascular disease, and endorsing satiety and weight loss [24]. Contempt their vast nutritious and medicinal benefits, research concerning screening new versatile prebiotics is unusual. Hence, more research would be focused on recognizing new health supplements, where showing novel prebiotics must be a prime concern.

1.4 Synbiotics

Progress in microbial research has ran to growth of synbiotics which is a combination of probiotics and prebiotics foodstuffs and helps in enhancing the survival and the im- plantation of live microbial dietary supplements in the gut [25]. The synergistic benefits are more efficiently promoted when both the probiotic and prebiotic work together in the living system. There is increasing scientific evidence that the symbiotic relationship between prebiotics and probiotics contributes knowingly to health. Commercial interest in practical foods containing synbiotics has consistently increased due to the awareness of the assistances for gut health, disease prevention and therapy. Research in this area

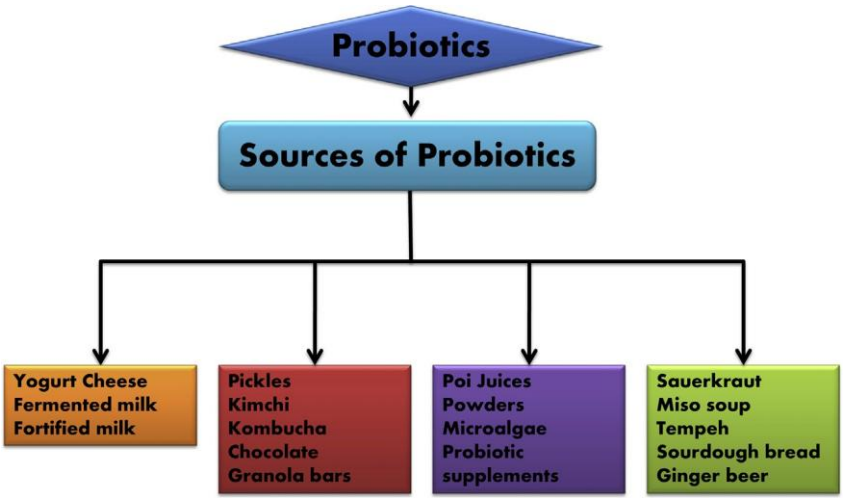

Fig. 1. Source of probiotics

is presently focused on emerging new health-promoting foods, as well as on choosing new cultures demonstrating an enhanced skill to colonize the human gut, along with their ability to digest new forms of prebiotics. Conventional trials and investigation have shown that the numerous beneficiary effects of probiotics, prebiotics, and synbiotics are much more effective than their unitary use known till date. Therefore, studies aimed at evolving new connection of probiotics and prebiotics are vital to exploit further potentials of enhancing nutritional and clinical health benefits.

Most probiotic microorganisms fit to Lactic Acid Bacteria (LAB), such as *Lactobacillus* spp, *Bifidobacterium* spp. and *Enterococcus* spp. The yeast *Saccharomyces boulardii* has been studied widely and also other bacterial species, like *Bacillus* spp. and *Clostridium butyricum* [35] Lactobacilli are Gram-positive bacteria, unable to sporulate, happening as rods or cocco- bacilli, with a GC composition of the genome usually below 50% (low GC bacteria). They are fastidious microorganisms, needing rich media to grow, and microaerophilic. The genus Lactobacillus belongs to the Phylum Firmicutes, Class Bacilli, Order Lactobacillales, Family Lactobacillaceae and its neighboring relatives, being grouped within the same Family, are the genera Paralactobacillus and Pediococcus. Some Lactobacillus cultures used as probiotic are *Lactobacillus Acidophilus, L. casei, L. delbrueckii, L. plantarum, L. rhamnosus* [36]. The genus Bifidobacterium, even if usually listed among LAB, is only poorly phylogenetically related to genuine LAB: it belongs to the Phylum Actinobacteria, Class Actinobacteria, Order Bifidobacteriales, Family Bifidobacteriaceae, its neighbor genera being Aeriscardovia, Gardnerella, Parascardovia, and Scardovia. The genus includes, at current, 30 species [36] Bifidobacteria are usual inhabitants of the human and animal gastrointestinal tract and is not astonishing to find them in mouth and feces. The intestinal tracts of newborns are colonized with Bifidobacterium within days after birth and the population is influenced by age, diet, antibiotics, and stress. The optimum pH for the growth of Bifidobacteria is 6–7 and virtually no development at below of 4.5 or above of 8.5. The optimum temperatures of growth are 37–41°C, the minimum is 25–28°C, and the maximum are 43–45°C. Some Bifidobacterium cultures used as probiotic are *B. adolescentis*, *B. longum*, *B. infantis*, *B. bifidum* and *B. breve* [37].

Table 1. Probiotic strains

Probiotic bacterial genera	Species	References
Lactobacillus	*L. plantarum, L. paracasei, L. acidophilus, L. casei, L. rhamnosus, L. crispatus, L. gasseri, L. reuteri, L. bulgaricus*	[26]
Bacillus	*B. coagulans, B. subtilis, B. laterosporus*	[27]
Lactococcus	*L. lactis, L. reuteri, L. rhamnosus, L. casei, L. acidophilus, L. curvatus, L. plantarum*	[28]
Enterococcus	*E. faecium*	[29]
Pediococcus	*P. acidilactici, P. pentosaceus*	[30]
Streptococcus	*S. sanguis, S. oralis, S. mitis, S. thermophilus, S. salivarius*	[31]
Bifidobacterium	*B. longum, B. catenulatum, B. breve, B. animalis, B. bifidum*	[32]
Bacteroides	*B. uniformis*	[33]
Saccharomyces	*S. boulardii*	[34]

Medical condition	Probiotics
Lactose maldigestion	LAB and *Streptococcus salivarius* subsp. *Thermophiles*
Antibiotic-associated diarrhea	LAB or *S. boulardii*
Traveler's diarrhea	LAB
Allergies	LAB
***Clostridium difficile*–induced Colitis**	LAB
Dental caries	LAB
Inflammatory bowel disease or irritable bowel syndrome	LAB and *Bifidobacterium* species, *S. boulardii* and drug, *S. boulardii* alone, or LAB alone
Cancer	LAB

1.5 Selection of Probiotic Strains

There are a number of conditions that must be met during the assortment of a probiotic bacterial strain with extreme importance placed on security issues. Strains of the *Lactobacillus* and *Bifidobacterium* genera are usually observed as safe from the basis of long-term human use. Associates of other genera such as *Bacillus licheniformis* have also been discovered to be used as probiotics. However, it should not be concluded that all members fitting to the *Bacillus* genus can be used as probiotics because there are some strains from the *Bacillus* genus that are related with diseases such as *Bacillus cereus*, which causes food-borne illnesses. It is perilous to perform safety assessment when the probiotics are not from the genera of *Lactobacillus* or *Bifidobacterium* (European Food Safety Authority [EFSA] 2007), [38].

Pathogenicity and infectivity, intrinsic properties as well as virulence factors related to destructiveness and metabolic activity of the microorganisms are structures that need to be communicated during the safety assessment process of probiotics [39]. Feasibility and action of probiotics during storage and when passing through the GIT is also essential. Stomach and the surroundings of the GIT have the highest acidity; consequently, it is serious to launch the conduct and fate of the microorganism during the passage through this condition. In vitro tests characteristically resembling the conditions in the GIT are normally used as a screening tool to classify potential probiotics. This is because colonization and potential health assistances can only be predicted when these viable cells are able to tolerate through the natural barriers that exist in the GIT such as low pH conditions and degradation by digestive enzymes as well as by bile salts [39,40]. The viable cell numbers of probiotics in a product should be at least 106 CFU/mL at the expiry date for health and functional claiming as the recommended minimum effective dose per day is 108–109 cells. Numerous factors such as pH, titrable acidity, molecular oxygen, redox potential, hydrogen peroxide, flavoring agents, packaging materials, and packaging conditions are associated with viable cell count of a microorganism in a product throughout the industrial and shelf-life periods [41]. Another significant selection criterion for a probiotic is the ability to adhere to host tissues chiefly to the intestinal mucus and epithelial cells to indorse efficient host-microbial interactions. This dealing is particularly important to prolong the holding period of the specific strain in the gut. However, continuous intake of orally directed probiotics is essential because enduring establishment of probiotics is uncommon. Many factors are involved in the adhesion of probiotic microorganisms to the host tissues. Microbial cell density, buffer components, fermentation duration, and growth medium are associated to the in vitro culture parameters while intestinal microflora, digestion, and the food matrix are referred to in vivo conditions [42] (Forssten *et al*. 2011).

There are ongoing studies on the identification of new strains for potential exploitation as probiotics concurrently with prevailing strains being explored for novel applications. These new strains need to be appraised and assessed based on established selection criteria which comprise safety and, functional and technological characteristics prior to the range of a particular strain for probiotic application.

1.6 Role of Probiotics

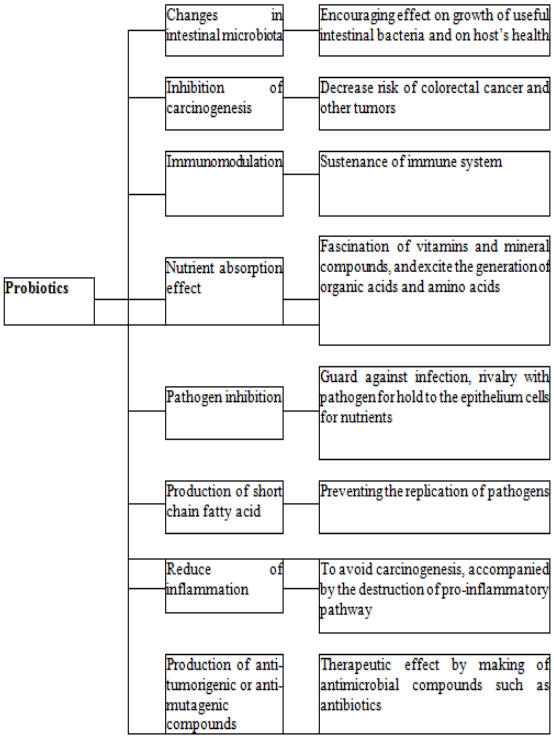

Fig. 2. Role of probiotics

1.7 Gastrointestinal Microbiota

The colonization of the human body through a varied microbiota, as well as the formation of a well-adjusted and diverse ecosystem, is a detailed process that requires a great deal of time. The gastrointestinal ecosystem is formed from the moment of birth and changes throughout the sequence of life. There are suggestions that already in the prenatal period, the microbiome begins to shape [43].

It is inclined by various adjustable (for example, diet, antibiotics) and non-modifiable issues (age, sex). The properties of their interaction may initiate colon tumors or provocative bowel diseases such as irritable bowel syndrome (IBS). This is a varied ecosystem which comprises more 10 to the power of 12 colony-forming unit per gram (CFU/g) satisfied belonging to about 1000 microorganism U species. Colon colonization by bacteria has a large influence on metabolic and enzymatic potentials. Bacteria partake in the absorption of many endogenous and exogenous compounds. Due to the microbial activity, many complexes are formed that affect the host's physiology in a helpful or harmful way [44]. The amount and the genus of bacteria in the gastrointestinal tract (GIT) are abridged in Table given below.

Table 2. The amount and types of microorganisms in the gastrointestinal tract (GIT) of human

Gastrointestinal Tract	Total Colonic Number (log CFU/mL)	Main Types of Microorganisms
Oral cavity	*10 to the power of 8*	*Streptococcus, Eubacteria, Capnocytophaga, Veillonella, Fusobacterium, Porphyromonas, Prevotella, Neisseria, Treponema, Lactobacterium, Eikenella, Leptotrichia, Peptostreptococcus, Propionibacterium, Rothia, Scardovia, Parascardovia, Alloscardovia, Candida, Saccharomyces, Penicillium, Scopularis, Aspergillus, Fusarium, Cryptococcus, Alternaria, Geotrichum*
Oesophagus	*10 to the power of 4-6*	*Streptococcus, Prevotella, Veillonella*
Stomach	*10 to the power of 2-4*	*Helicobacter (species pylori), Lactobacillus, Staphylococcus, Streptococcus, Clostridium, Capnocytophaga, Deinococcus, Veillonella, Escherichia, Bifidobacterium, Prevotella, Caulobacter, Actinobacillus, Corynebacterium, Rothia, Gemella, Leptotrichia, Porphyromonas*
Duodenum	*10 to the power of 3*	*Enterococcus, Lactobacillus, Bacteroides, Bifidobacterium, Clostridium, Enterobacteriaceae, yeast*
Jejunum	*10 to the power of 4*	*Enterococcus, Lactobacillus, Bacteroides, Bifidobacterium, Clostridium, Enterobacteriaceae, yeast*
Ileum	*10 to the power of 7*	*Enterococcus, Lactobacillus, Bacteroides, Bifidobacterium, Clostridium, Enterobacteriaceae, yeast*
Large intestine	*10 to the power of 10–11*	*Enterococcus, Lactobacillus, Bacteroides, Fusobacterium, Bifidobacterium, Clostridium, Enterobacteriaceae, Peptococcus, Peptostreptococcus, Staphylococcus, Ruminococcus, Eubacterium, Streptococcus, Actinomyces, Finegoldia (species magna), Micromonas (species micros), Peptococcus (species niger), Veillonella, Escherichia (species coli), Klebsiella, Proteus, Pseudomonas, Enterococcus (species faecalis), Bacillus*
Rectum	*10 to the power of 11–12*	*Enterococcus, Lactobacillus, Bacteroides, Fusobacterium, Bifidobacterium, Clostridium, Enterobacteriaceae, Peptococcus, Peptostreptococcus, Staphylococcus, Ruminococcus, Eubacterium, Streptococcus, Actinomyces, Finegoldia (species magna), Micromonas (species micros), Peptococcus (species niger), Veillonella, Escherichia (species coli), Klebsiella, Proteus, Pseudomonas, Enterococcus (species faecalis), Bacillus*

2. PROBIOTICS AND CANCER

Table 3. General effects of probiotics on cancer cells in vitro

Probiotic strain/details of experiment	Cell line	Effect	References
Bifidobacterium adolescentis SPM0212 /cell free supernatant used/	Caco-2, HT-29, SW480	↓ Cell proliferation	[45]
Enterococcus faecium RM11 *Lactobacillus fermentum* RM28	Caco-2	Cell proliferation: ↓ 21% ↓ 23%	[46]
Lactobacillus rhamnosus GG *Bifidobacterium lactis* Bb12	Caco-2	↑ Apoptosis	[47]
Bacillus polyfermenticus	HT-29, DLD-1, Caco-2	↓ Cell proliferation N/E on apoptosis	(Ma, EL et al, 2010)
Bacillus polyfermenticus /AOM stimulation	NMC460	↓ Cell colony formation in cancer cells (N/E on normal colonocytes)	(Ma, EL et al,2010)
Lactobacillus paracasei IMPC2.1 *Lactobacillus rhamnosus* GG /heat killed/	DLD-1	↓ Cell proliferation Induction of apoptosis	[47]
Pediococcus pentosaceus FP3, *Lactobacillus salivarius* FP25/FP35, *Enterococcus faecium* FP51	Caco-2	↓ Cell proliferation Activation of apoptosis	[49]
Lactobacillus plantarum A7 *Lactobacillus rhamnosus* GG /heat killed, cell free supernatant used/	Caco-2, HT-29	↓ Cell proliferation	[50]
Clostridium butyricum ATCC *Bacillus subtilis* ATCC 9398	HCT116, SW1116, Caco-2	↓ Cell proliferation	[51]
Bacillus polyfermenticus KU3	LoVo, HT-29, AGS	>90% ↓ Cell proliferation	[52]
Lactococcus lactis NK34	HT-29, LoVo, AGS	>80% ↓ Cell proliferation	) [53]
Lactobacillus casei ATCC 393	HT29 and CT26	Induction of apoptosis	[54]
Lactobacillus pentosus B281 *Lactobacillus plantarum* B282 /cell free supernatant used/	Caco-2 and HT-29	↓ Cell proliferation Cell cycle arrest (G1)	[55]

3. PROBIOTICS IN TREATMENT AND PROPHYLAXIS

Table 4. Comparison of the strategies using the probiotic strains in cancer prevention and treatment

Probiotic strains	Model	Treatment	Effect	References
Probiotic vaccination *Lactococcus lactis*	C57BL/6 mice → Intranasal	E7 protein displayed	↑ Antitumor effect of following Ad-CRT-E7 treatment	[56]
Lactococcus lactis	C57BL/6 mice → Intranasal	E7 protein displayed	HPV-16 E7-specific immune response	[57]
Bifidobacterium longum	C57BL/6N mice inj/w C1498-WT1 → Oral	WT1 displayed	↓ WT1-expressing Tumor growth ↑ Survival rate ↑ Tumor infiltration of CD4+ T and CD8+ T ↑ Cytotoxic activity	[58]

Probiotic strains	Model	Treatment	Effect	References
Mitigation of inflammation				
Streptococcus thermophilus Lactococcus lactis	BALB/c mice (DMH)-I CRC → Oral	Antioxidant enzymes (catalase, superoxide dismutase), IL-10; Groups: IL-10 (SICE) IL-10 (cDNA) antioxidants, mix	All groups: ↓ Tumor incidence ↓ ACF and MPL ↓ MCP-1 ↑ IL-10/TNFα Groups: IL 10 (SICE), antioxidants and mix: no tumor Mix: ↓↓ ACF and MPL ↓↓ MCP-1 ↑↑ IL-10/TNFα	[58]
Lactococcus lactis	DSS-induced mice → Intragastric	IL-10	No tumor ↓ Colonic damage ↓ Inflammation	[59]
Lactococcus lactis	BALB/c mice (DMH)-I CRC → Oral	Catalase	↓ Colonic damage ↓ Inflammation ↓ Tumor incidence ↓ Tumor progression	[60]
Drug delivery				
Bifidobacterium longum	BALB/c mice inj/w CT24 → Oral or injection	Tumstatin	Antitumor effect	[61]
Lactococcus lactis	Rats (DMH)-I CRC → Oral	Endostatin	↑ Survival rate N/E on complete cure	[62]
Bifidobacterium longum	C57BL/6 mice inj/w Lewis lung cancer and B16-F10 → Oral	Endostatin or endostatin + selenium	Endostatin group: ↓ Tumor progression ↑ Survival time Endostatin ± selenium: ↓↓ Tumor progression ↑ Activity of NK, T cells and ↑ Activity of IL-2 and TNF-a i	[63]
Gene therapy				
Bifidobacterium infantis	Melanoma B16-F10 cells → Supernatant fluid	Cytosine deaminase/5-fluorocytosine	↑ Morphological damage ↓ Growth	[64]
	C57BL/6 Mice, inj/w B16-F10 Cells → Injection	Cytosine deaminase/5-fluorocytosine	Antitumor effect	
Bifidobacterium infantis	BALB/c Mice and cell lines: Colo320, MKN-45, SSMC-7721, MDA-MB-231 → Injection	Thymidine kinase (BF-rTK) Ganciclovir (GCV)	↑ Mitochondrial apoptosis ↓ Inflammation ↓ TNFα	[65]

3.1 Mechanisms of Probiotic Activity

Probiotics have numerous mechanisms of action although the exact manner in which they exert their effects is still not fully explained. These range from bacteriocin and short chain fatty acid production, letting down of gut pH, and nutrient competition to stimulation of mucosal barrier function and immunomodulation. then final in particular has been the topic of plentiful studies and there is substantial evidence that probiotics affect several aspects of the acquired and innate immune response by coaxing phagocytosis and IgA secretion, modifying T-cell responses, ornamental T1 responses, and weakening T2 responses [66].

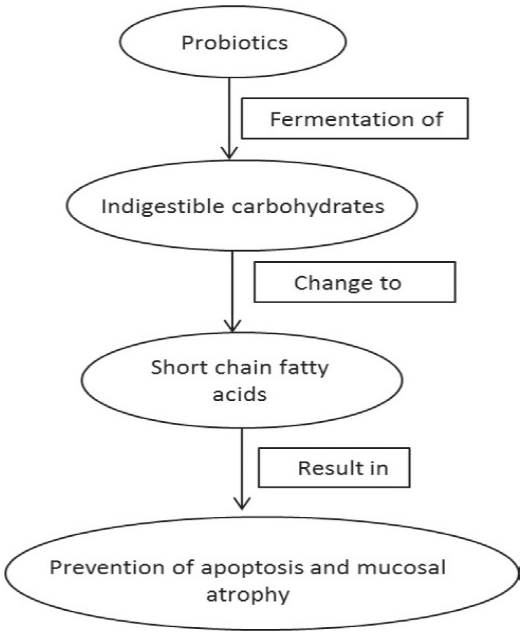

Fig. 3. Mechanisms of Probiotics

3.2 Mechanisms of Anti-carcinogenicity

3.2.1 Binding of carcinogens

There are a bulky number of reports describing the adsorption or binding in vitro by LAB and other intestinal bacteria, of a variety of food-borne carcinogens including the heterocyclic amines formed on the time of cooking of meat, the fungal toxin Aflatoxin B1, benzo(a)pyrene. In several of these studies, a concomitant decrease in mutagenicity was reported [67].

3.2.2 Effects on bacterial enzymes

The capability of the colonic microflora to generate a wide variety of mutagens, carcinogens and tumor agents from dietary and endogenously-produced precursors is well.

For example, the enzyme ß-glucuronidase is intricate in the release in the colon, from their conjugated form, of a number of dietary carcinogens, with polycyclic aromatic hydrocarbons. Species of Bifidobacterium and Lactobacillus, have low activities of these enzymes involved in carcinogen formation and metabolism by comparison to other major anaerobes in the gut such as Bacteroides, eubacteria and clostridia. This proposes that cumulative the share of LAB in the gut could adapt, helpfully, the levels of xenobiotic processing enzymes [67].

3.2.3 Enhancement of the host's immune response

One elucidation for tumor destruction by lactic acid bacteria may be that it is arbitrated via an immune response in the host. Sekine et al, suggested that *B. infantis* rouses the host- mediated response, leading to tumor suppression or regression. In count, there are studies to propose that lactic acid bacteria play an vital role and function in the host's immunoprotected system by increasing specific and non-specific mechanisms to employ an anti-tumor effect [68].

3.2.4Gut Microbiota as a Tumor-Suppressor

Gut microbial populace may disturb pathological processes, such as cancer genesis and development, either in a positive or in a negative way, reliant on its own configuration. Curiously, a number of microbes-derived molecules show an anti-tumor activity. In certain, microbial-derived SCFAs may have an anti-cancer effect. For example, gut bacterial butyrate and propionate are able to inhibit host's tumor cells histone deacetylases with a general anti-cancer effect. Such mechanism is the reason of the anti-tumoral in vitro and in vivo effect of butyrate observed in both colorectal cancer (CRC) and lymphoma (Jan et al, 2002).

Table 5. Probiotics and decreases bacterial enzymes

Enzymes	Probiotic	Result
Faecal ß-glucuronidase	*L. acidophilus* (109-1010 cells/day)	Reduced the activity of ß-glucuronidase by 40-50%
ß-glucuronidase and ß-glucosidase activity	*L. acidophilus* or *B. adolescentis* (109cells/day for three days)	A important reduction in enzyme activity for *L. acidophilus* only
Faecal enzymes and ammonia	B. longum (freeze dried) and inulin (5%)	Significant decrease in ß-glucuronidase and ammonia.
Faecal levels of enzyme	*L. acidophilus*	Animals given *L. acidophilus* had significantly lower free amines in faeces and 50% less of conjugates

Some of the probiotics derivative molecules and metabolites are able to modulate host's immune system, thereby triggering an indirect immune-mediated response against tumor development. For example, the widely studied bacterial lipopolysaccharide (LPS), a chief constituent of the outer membrane in gram-negative bacteria, triggers the host's cell surface receptor toll-like receptor 4 (TLR4), fitting to the family of pattern recognition receptors (PRRs), thus actuating immune T cell-mediated response against cancer cells [69]. In the comparable way, the monophosphorylate lipid A (MPL) from *Salmonella enterica* has been currently used as adjuvant in the vaccine formulation used against anti-cervical carcinoma [70] Moreover, bacteriological derived pyridoxine, a group B vitamin, can excite host's antitumoral immune surveillance [71]. The administration of such probiotics, as for example Mutaflor (*Escherichia coli* Nissle 1917) [72] collective with the intestinal antibiotic rifaximin, demonstrated a clear anti-inflammatory activity, enhancing the anti-inflammatory consequence of rifaximin in a rat model of inflammatory bowel disease [73]. Moreover, several probiotics have shown a potential antineoplastic activity. For example, probiotics or probiotics-derived metabolites administered to mice can, in turn, to inhibit tumor growth. One good example is ferricrome metabolite concealed from *Lactobacillus casei*, able to trigger apoptosis in tumor cells via JNK pathway direct activation [74] It has been also reported in numerous studies that Lactobacilli may stimulate host's immune cells such as NK cells or dendritic cells (DC) or TH1 response, which, in turn, leads to the abolition of cancerous or precancerous cells, although the exact bacterial bioproduct arbitrating such stimulatory effect still needs to be identified [75].

Anti-tumoral effects of the gut microbiota. Probiotics and other gut resident bacteria are able to secrete molecules, capable, in turn, to bout tumor growth and stop tumorigenesis through numerous mechanisms. Schematic of the intestinal layers, from top to bottom: mucus and microbiota, gut epithelium. Into the grey boxes are illustrated, from top to bottom, the microorganism species implicated in the anti-cancer process, the molecules formed and the consistent effects induced within the host. Abbreviations: MPL, mono phosphoryl lipid A; LPS, lipopolysaccharide.

3.2.5 Gut microbiota as a tumor-promoter

Gut dysbiosis and the consequential development of pathogenic populations within the gut microbiota, may donate to a wide variety of pathologies, even in sites distant from the gut, fluctuating from bowel inflammation, to neurodegenerative diseases (including Parkinson's disease) and cancer [73]. Concerning cancer, within a symbiotic gut, convinced bacterial pathogens can negatively disturb either the host's metabolism or the host's gut and immune system functionalities, thereby triggering tumor growth [76]. Importantly, gastro-intestinal dysbiosis has been linked with mutually local and distant tumors [77]. Microbial pathogens are known to drive the 20% of tumorigenesis and a greater number of malignancies are associated with microbial commensal imbalance, or dysbiosis (Bhatt *et al*, 2017) Even though only *Helicobacter pylori* is included among class I

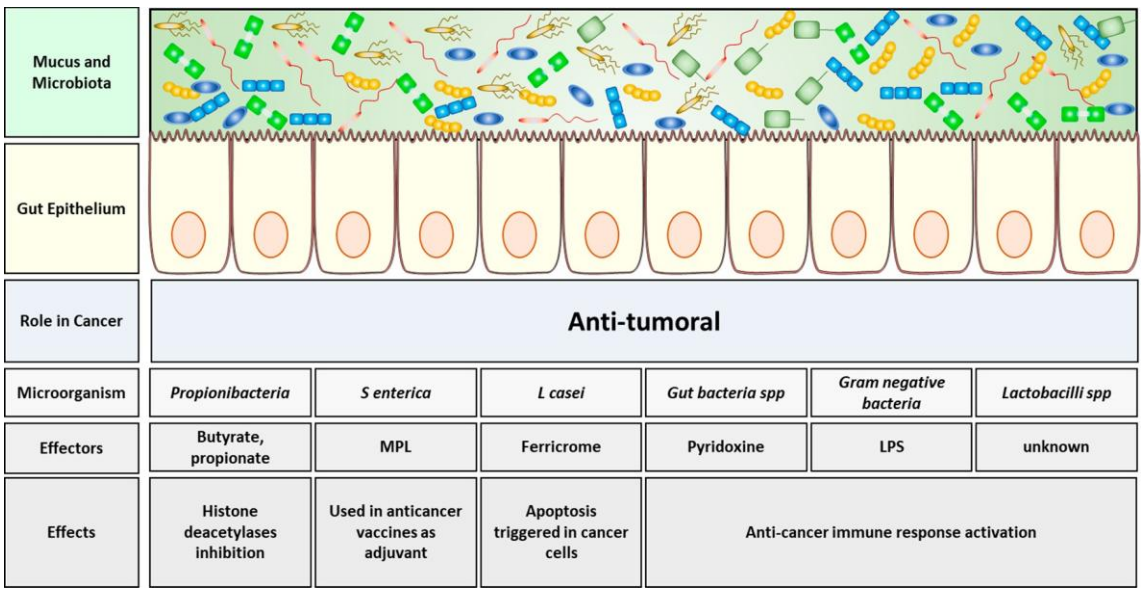

Fig. 4. Anti-tumoral role of probiotics

carcinogens by the World Health Organization (WHO) [78], numerous studies performed in cell culture and animal models, assessed the skill of additional microbiota populations to affect host's DNA replication and integrity [79]. In fact, during pathogenic infections, when the gut microbiome is affected by dysbiosis, bacterial pathogens can enlarge and release a large amount of toxins which, in turn, induce host's DNA breaks, thus contributing to genomic instability, tumor initiation and progression in those predisposed cells [80]. This is the situation of colibactin and cryptolectal distending toxin (CDT) both produced by *Escherichia coli* and displaying a DNAse activity. Once released in the nearness of the gastrointestinal epithelium, the toxins produce DNA double-strand breaks within the host's epithelial cells, thus indorsing a transient cell cycle arrest, allowing for genomic mutations to arise, and finally leading to tumor construction [81]. Gut pathogenic bacteria can also delay with DNA damage response and repair pathways, as in the case of *Shigella flexneri*, inducing host's cells p53 degradation via the exudation of its enzymes inositol phosphate phosphatase D (IpgD) and cysteine protease-like virulence gene A (VirA), therefore collective the probability of awarding mutations during the DNA damage response in diseased cells [82]. In the same way, the product of the cytotoxin associated gene A (CagA) from *Helicobacter pylori*, encourages the proteasome-mediated degradation of p53 in gastric epithelial cells, by intrusive with the host's AKT pathway, thus encouraging the upsurge of gastric cancer [83].

Furthermore, gut bacteria can modify numerous host's cellular proliferative and pro-survival pathways, therefore causative to cancer. For example, *Helicobacter pylori* derived CagA protein, *Fusobacterium nucleatum* effecter adhesin A (FadA) and *Bacteroides fragilis* metalloproteinase toxin (MP toxin) are all accomplished to interact (directly or indirectly) with the host's epithelial E-cadherin, thus disrupting the intercellular connections and actuating β-catenin signaling. This, in turn, triggers cell propagation and the potential cancerogenic alteration of those exaggerated host's cells (Murata-Kamiya *et al*, 2007). In the similar direction, the *Salmonella enterica* effector a virulence protein A (AvrA) is able to translocate into host's cells and activate β-catenin via its intrinsic de-ubiquitinase activity [84]. As for the β-catenin signaling, other virulency factors out in the extracellular gut milieu during a pathogenic infection, can possibly induce cancer transformation when contaminating pre-transformed cells, through the instigation of other pro-survival intrinsic host's cellular pathways, such as MAPK and AKT, as for CagA from *Helicobacter pylori*, controlling the hosts MAPK pathway or AvrA from *Salmonella enterica*, triggering both MAPK and AKT pathways (Bronte-Tinkew *et al*, 2009). In specific, CagA from *Helicobacter pylori* can dilemma many host's proteins intracellularly, including the protein tyrosine phosphatase SHP-2. CagA-SHP-2 complex formation deregulates the phosphatase activity of SHP-2, which, in turn, approves Ras/MAPK signaling initiation [85]. Also, infective bacteria may circuitously affect host's tumorigenesis. Varied mechanisms can mediate this effect. One is the cohort of oxidative stress, leading to cell autonomous genomic mutations [86]. Another one contains either in the enrichment of the inflammation or the embarrassment of the host's immune response, thus helping the tumor immune-escape [87]. For example, *Helicobacter pylori* or *Bacteroides fragilis* are both able to activate the host's spermine oxidase, which, in turn, generates hydrogen peroxide and reactive oxygen species (ROS)-induced accretion of DNA damage [88]. *Enterococcus faecalis* produces extracellular superoxide and derivative oxygen species is capable to diffuse into host's cells. In turn, the increase in the oxidative milieu increases the possibility of host's cellular DNA mutations [89]. Additionally, related bacteria can excite cancer formation by blocking immune-effectors that normally inhibit tumorigenesis. For example, *Fusobacterium nucleatum* inhibits for its own advantage host's Natural Killer (NK) cells, in order to recruit at the site of the infection myeloid suppressor cells, therefore indirectly helping cancer genesis. Such mechanism is mediated by the bacterial virulence factor Fap2, able to bind and block the NK inhibitory receptor TGIT, thus arresting the NK-mediated tumor cell attack [90]. Finally, certain microbiota species may restrict with host's hormones metabolism. In fact, it has been widely studied the link between bacterial secretion of the β-glucuronidase enzymes and the amplified bioavailability of the host's estrogen hormones (both originating from hepatic catabolism and phytoestrogens). When gut dysbiosis is coupled with an increase in the β-glucuronidase-secreting bacteria, such as *Clostridium leptum* and *Clostridium coccoides*, the enzyme deconjugates liver-catabolized and plant-derived estrogens, enabling them to bind and trigger the estrogen receptors expressed by target cells [91]. Estrogen receptors activation promotes cell proliferation in tissues responding to estrogens, as breast and endometrium [92]. Accordingly, this augmented intake of estrogen hormones is related with an amplified risk of emerging breast cancer, supporting the discovery that the gut microbiota configuration of women with breast cancer differs from that from healthy controls, and signifying that several gut bacteria, which could be over-expressed during dysbiosis, may be related with breast cancer growth [93].

Though there are notable examples of infective microbiota capable of cheering oncogenesis through the modulation oncogenic host's cell pathways or by intrusive either with the host's hormonal or the host's immune system, no strong bacterial oncogenic driver has been identified yet. In particular, it is hard to clearly regulate whether microbiota changes might affect cancer genesis or the conflicting [94]. Also, vicissitudes in the host's lifestyle, diet and immune system are among the factors which intensely impact the microbiota composition and activity [95]. Moreover, the very same anti-cancer action might shape the patient's microbiome and, at the same time, host's specific microbiome can deeply disturb patient's reply to therapy. Lactic acid bacteria or a soluble compound formed by the bacteria may relate directly with tumor cells in culture and constrain their growth. Lactic acid bacteria significantly abridged the growth and feasibility of the human colon cancer cell line HT-29 in culture, with a important increase in dipeptidyl peptidase IV and brush border enzymes, suggesting that these cells might have entered a difference process. Milk fermented by *B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei* repressed the growth of the MCF7 breast cancer cell line, the antiproliferative effect not being related to the presence of bacteria. These findings suggest the presence of an ex novo soluble compound produced by lactic acid bacteria during milk fermentation or the microbial transformation of some milk apparatuses in a biologically active form [96].

Pro-tumoral effects of the gut microbiota. Bacteria prominent during gut dysbiosis can conceal toxins able to interfere with host cell growth, finally inclining the host organism to cancer development. Diagram of the intestinal layers, from top to bottom: mucus and microbiota, gut epithelium. Into the grey boxes are illustrated, from top to bottom, the microorganism species concerned in the pro-cancer process, the molecules produced and the corresponding effects persuaded within the host. Abbreviations: ROS, Reactive Oxygen Species; CTD, cytolethal distending toxin; IpgD, inositol phosphate phosphatase D; VirA, virulence gene A; CagA, cytotoxin associated gene A; FadA, Fusobacterium effector adhesin A; MP Toxin, metalloproteinase toxin; AvrA, avirulence protein A; β-gluc, β-glucuronidase.

Helicobacter pylori produced protein CagA was the initial bacterial protein shown to be involved in human cancer [97].

3.3 Anti-Cancer Therapy

Anti-cancer therapies are intended with the final goal of being active in the eradication of the targeted malignancy. Since nearly every available anti-cancer action is toxic also towards normal cells, their use may be combined with side effects, some of which can conciliation the overall endurance of the patients [98]. Also, tumors are essentially complex: as they challenge to accrue mutations, cancers progress and adapt to the hosting organism [99]. In component, cancers initiate from the stochastic acquisition of driver mutations within genes intricate in key processes, with DNA duplication, DNA repair, oxidative stress response. Such accumulation finally lets the transformation of a normal cell into a malignant one [99]. Both the commencement and the progress of a tumor may be viewed as a blended impairment of such fundamental cellular processes,

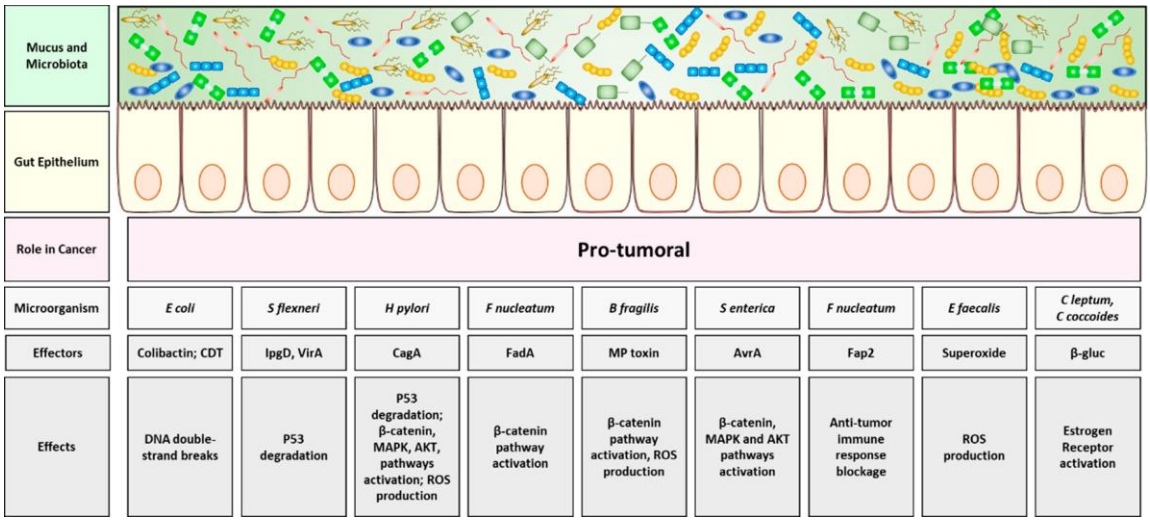

Fig. 5. Pro-tumoral role of probiotics

meaning that from one original cancer cell might rise a molecularly diverse bulk tumor made of several clones of cancer cells, each one revealing a differential intrinsic sensitivity to the anti-cancer therapies [100]. This assortment derives from intrinsic tumor cellular genomic randomness, vacillating from microsatellite unpredictability (due to impairments of the DNA mismatch repair system) to chromosomal instability (arising from segregation errors during cell mitosis) [101]. On maximum of that, such genetic mechanisms might be tied with epigenetics, transcriptional and post-transcriptional intracellular changes, lastly leading to a growing tumor complexity, through time and space [102].

Importantly, this intra-tumoral variety is resolutely linked with the progress of the resistance to therapy, measured the first cause of failure of the manageable anti-cancer treatments, as well as subsequent tumor relapses [103]. To contest such resistance, combined therapies and personalized approaches, based on the exact genetic features of the malignancy, are in constant progress [103]. Emerging malignant cells not only are exposed to their intrinsic heterogeneity, also they are acquainted and eradicated by the host's immune system [104]. On their side, tumor cells, thanks to their genetic instability, continually evolve novel strategies to escape from such immunosurveillance and expand within the host [104]. Along with chemotherapy and radiotherapy, a novel anti-cancer approach is considered the so-called targeted immunotherapy, bearing the dual role of both boosting the host anti-tumor immune response, and, at the same time, helping to hit cancer resistance and recurrence mechanisms [105].

Modifying gut microbiome may extremely influence the consequence of anti-cancer therapies. In fact, radiotherapy, chemotherapy and immunotherapy behaviors can all modify patients' microbiome and, at the same time, microbiome configuration can deeply affect patients' response to such treatments [106]. It is therefore vital to recognize which are the aspects able to impact the gut microbiome and, in turn, to discovery novel strategies to employ the gut microbiome, with the chief goal of finally humanizing patients' therapeutic outcome. Specifically, interventions on microbiome may be pivotal to ameliorate anti-cancer therapy-related toxicity, as well as to progress anti-cancer therapy efficacy [107]. Posterior in 1890 two heat-inactivated microorganisms (*Streptococci*) were inoculated intratumorally for the very first time in humans as an effort to cure cancer [108]. Also, several periods later, *Mycobacterium bovis* was successfully injected into bladder in patients, following the resection of a bladder tumor. It has been observed that the bacteria, by encouraging a local immune response, helped to reduce the relapse of the tumor [109]. Moreover, it has been revealed how oral administration of *Lactobacillus casei* abridged superficial bladder cancer reappearance (Aso and Akazan, 1992). The machinery behind involves the direct bacterial stimulus of host's NK cells and macrophages, in turn accountable of a strong antitumoral immune response [110].

These explanations paved the way for several published, as well as enduring, clinical trials, based on the practice of gut bacterial weakened strains in anti-cancer therapy. These trials are peeling light on the key role of such bacteria on triggering anti-tumor immune response [111]. For example, it has been observed that the intradermal injection of *Mycobacterium obuense* in melanoma and in pancreatic ductal carcinoma activates antitumoral immune response, acting on host's antigen presenting cells (APCs) and cytotoxic T cells [112]. Additional clinical trials further exposed how attenuated bacteria vaccinated directly into the tumor mass are able to both stimulate anti-tumoral immune response and also have a direct cytotoxic effect on the tumor cells, because their capability of inhabiting tumors, as pragmatic in several different refractory solid tumor studies, towards the administration of attenuated and/or genetically modified *Salmonella typhimurium* [113]. Although these results are encouraging, numerous clinical trials are currently ongoing in order to ameliorate the patients' clinical consequences, given bacteria-associated toxicity, mostly correlated to their long half-life [114].

Role of probiotics in anti-cancer therapy. Probiotics and Fecal Microbiome Transplantation (FMT) are currently studied as anti-cancer adjuvants to fight dysbiosis following anti-cancer therapy, to upsurge chemotherapy and immunotherapy efficacy and to both decrease tumor mass and avoid tumor recurrence

3.4 Modulation of Gut Microbiota to Enhance Chemotherapy and Immunotherapy Efficacy

The microbiota, when affected by dysbiosis, can deeply affect both cancer pathogenesis and its therapeutic outcome. In particular, the regulation of such therapeutic result is tightly connected with the capability of the gut microbiota to absorb anti-tumoral compounds, as well as to modulate host's immune response and swelling pathways [115]. These two effects combined together may explain the robust involvement of the patient's microbiome composition in affecting the efficacy of both chemotherapy and immunotherapy with respect to chemotherapy, it has

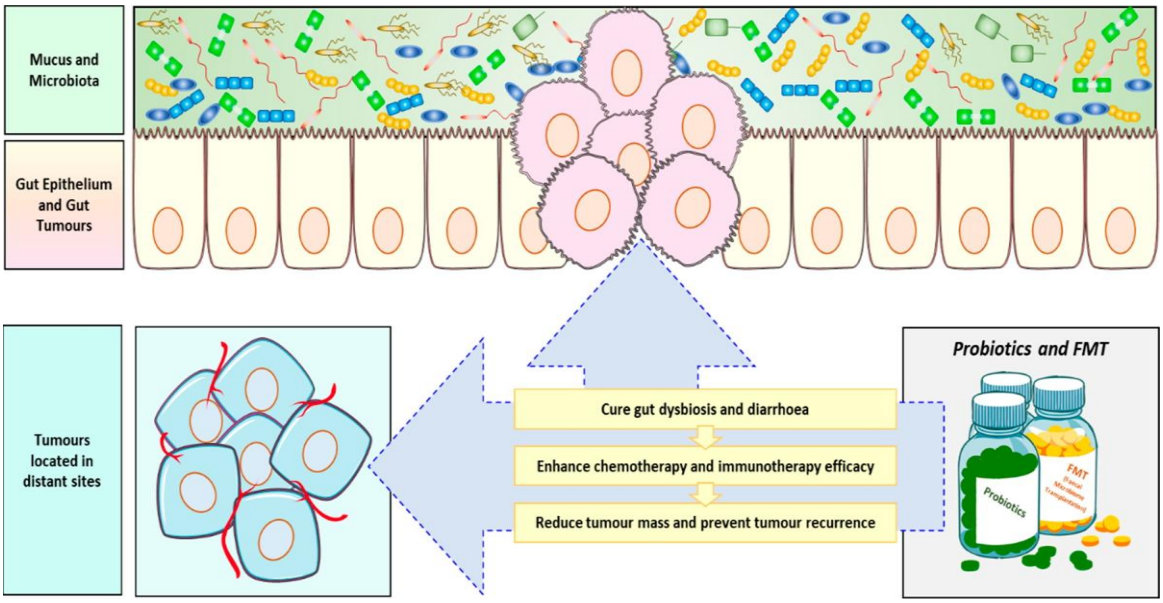

Fig. 6. Role of probiotics in gut

been described how tumor-bearing mice, whichever germ free or having their gut microbiota depleted after antibiotics therapy, do not respond to oxaliplatin drug treatment. The description is that commensal microbiome members within the gut of the mice might produce TLR agonists, thus sanctioning the rise of an oxidative stress milieu and tumor cell death. As a direct consequence, without a healthy gut microbiota there is a decreased microbiota-dependent ROS production, thus a less active chemotherapeutic response [116] reliably, mice bearing lung tumors treated with cisplatin coupled with antibiotics, survive less and develop bigger tumors. If cisplatin is combined with probiotics, such as *Lactobacilli*, mice show an improved response to therapy. The mechanism involves the initiation of pro-apoptotic genes within the tumor mass and the enhancement of host's immune response [117].

Additional extensively used anti-cancer molecule, cyclophosphamide, joined with oral bacterial management (*Lactobacillus johonsoni* and *Enterococcus hirae*), mains to the conversion of T cells from immature to pro-inflammatory T helper 17 (TH17), with the concluding effect of improving cyclophosphamide efficacy in tumor-bearing mice [118].

With orientation to immunotherapy, the administration of CpG oligodeoxynucleotides, synthetic molecules mimicking bacterial DNA, sturdily rouse the immune system, consequently showing anti-tumor activity in several cancers [119]. Along this line, the intra-tumoral injection of CpG oligodeoxynucleotides administered together with an anti-interleukin-10 receptor (IL-10R) antibody, induce TNF construction from tumor infiltrating myeloid cells and, in turn, decrease the growth several types of tumors in mice (Lida *et al*, 2013). Moreover, the management of a specific bacteria, Alistipes *shahii*, to antibiotic-treated tumor bearing mice, restores TNF production with a notable improvement in the therapeutic outcome (Lida et al, 2013). Given the array of effects that gut microbiome may play on the host's immune system, it is not amazing that developing studies strongly linked the patients' microbiome conformation with the inherent efficacy of immune checkpoint inhibitors-based immunotherapy, in the treatments of different solid tumors [120]. Immune checkpoint embarrassment consists in the management of therapeutic agents able to chunk the immune-inhibitory pathway, thus modulating T cell initiation against tumor target cells. The currently marketed checkpoint inhibitors are in monoclonal antibodies targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4) or the programmed death 1 (PD1) located on T cell surfaces, or its ligand, programmed death ligand 1 (PD-L1), expressed by the APCs [21] While CTLA-4 regulates T cells proliferation early in the immune response within the lymph nodes, PD-1 suppresses T-cell activation later, within the body periphery [122].

A few years ago, two studies suggested the potential involvement of the gut microbiome in modulating the efficacy of such anti CTLA4 and anti-PD1 based therapies [123].

Vetizou et al. demonstrated that the efficacy of anti-CTLA4 antibodies in reducing sarcoma tumor growth

in mice is significantly enlarged when the gut microbiome is enriched in *Bacteroides fragilis* and *Burkholderia cepacia* [123].

On the same line, Sivan et al, found that the effectiveness of PD-L1 targeting-antibody in the cure of melanoma in mice is improved in the presence of gut microbiome enriched in *Bifidobacterium* species [124]. In detail, they confirmed that oral administration of a cocktail of *Bifidobacterium* species joint with the anti-PD-L1 antibody, specifically boosts T cell response and chunks the melanoma growth [124].

Multiple translational studies, published in 2018, further support the essential role of the gut microbiome in moderating the response to resistant checkpoint blockade [120]. In particular, [120] originate that melanoma patients treated with antibiotics along with the anti-PD1/anti-PD-L1 immunotherapy had a lesser survival rate. Prominently, metagenomics analysis of patients' fecal gut microbiome showed a alteration in the configuration of their gut microbiome. Anti-PD1 responders were augmented in two phyla (*Akkermansia* and *Alistipes*). Performing FMT from patients to germ free mice, the authors found that *Akkermansia muciniphila* (alone or in combination with *Enterococcus hirae*) was able to increase intra-tumoral cytotoxic T cell infiltrates, thus increasing the PD-1 blockade reply in mice [120]. In similar, Gopalakrishnan et al. (Gopalakrishnan *et al*, 2018) demonstrated through metagenomics analysis of melanoma patients' fecal samples that the anti-PD1 responders' microbiome was different in composition compared with that of non-responders. The authors observed in patient's gut microbiome an increase in the abundance of *Clostridiales*, *Ruminococcaceae* and *Faecalibacteriae*. Functional studies performed with FMT in germ free mice further demonstrated how treating mice with the identified bacteria, along with the anti-PD1 therapy, enhanced the anti-cancer effects and reduces the melanoma growth [125].

Along the same line, Matson et al. [126] did a metagenomics characterization of stools samples from melanoma patients treated with immune checkpoint inhibitors, additional corroborating the verdict that responders showed a different microbiome linked to those not responding to therapy. They recognized and functionally proven in vivo the reputation of *Bifidobacterium longum*, *Enterococcus faecium* and *Collinsella aerofaciens* in ameliorating anti-PD-L1 efficacy [126].

Although the immune checkpoint inhibitors have victory in treating various menaces, there is still a significant number of patients that can use such therapy only for a partial amount of time, given the existence of strong toxic side effects, with gut inflammation, due to the succeeding immune-dysregulation (i.e, autoimmunity) [127]. In animals, oral gavage of *Bacterioides fragilis* and *Burkholderia cepacia* recognized an amelioration of such immunotherapy-associated toxic side effects [123]. In line with this observation, it has been seen that patients treated with anti-CTLA4 antibody, poisonous side effects are facilitated by an increased abundance of Firmicutes, such as *Faecalisbacterium*, and a decreased abundance of *Bacterioides* [128]. Altogether, these data offer a strong evidence of the character of gut microbiota composition in modulating the consequence of both immunotherapy comeback and toxicity.

Even if the last span witnessed massive advances in first appearance of the role of gut microbiome in cancer and other diseases, there are still numerous obstacles for decoding basic microbiome research into therapeutic applications. Mid the gut bacteria can develop potential pathogens and that might bound, or at least slow down, the transformation of the in vitro and in vivo consequences to the clinic. In light of the novel instructions described above, any antibacterial therapy varying the intestinal equilibrium, done anti-cancer therapy, needs to be wisely assessed. In detail, the heterogenous patients' microbiome can either be harmful or beneficial to tumor progression and therapy, dependent on its composition and prevailing species. As further considered, looking at the belongings of probiotics dealings in anti-cancer therapy, it might be essential in the future to trail a adapted approach, based on the precise patient's microbiome configuration.

3.5 Anti-cancer Activity of Probiotics

In concern WHO says that (WHO, 2017), cancer has been a appalling disease troubling peoples all over the globe and about 14 million new cases and 8.2 million cancer-related deaths additional till 2012. More than 70% of the worldwide cancer demises are from Asian, African, and American continents [129]. In this time, concentrated research on cancer concerning Genomics, proteomics, and molecular pathology, has heightened the consociate about cancer and public consciousness. Many new drugs using nanotechnology and biotechnology (nanocapsule) with charming properties have been exposed but still tolerance to their problem and side effect has been a chief limitation to it. Natural sources that confer anti-carcinogenic effects, such as probiotics have been receiving chief attention in recent years [130]. They have grew interest from clinical nutritionists, scientists, and industrialists to work in a

collaborative manner to bring down the disease and mature an effective drug with minimal or no side-effects [131].

In vitro studies have established that probiotic strains, *Lactobacillus fermentum NCIMB-5221* and -8829, have probable in suppressing colorectal cancer cells and endorsing normal epithelial colon cell growth through the invention of SCFAs (ferulic acid). This capability was also associated with other probiotics namely *L. acidophilus* ATCC 314 *and L. rhamnosus ATCC 51303* both of which were earlier characterized with tumorigenic activity [132].

Two diverse probiotic strains *L. acidophilus LA102 and L. casei LC232* have also been invent to show pronounced cytotoxic activities, with in *vitro* anti-proliferative activity against two colorectal cancer cell lines (Caco-2 and HRT-18) [133]. Though probiotics could play a significant role in neutralizing cancer, research is partial only to *in vitro* tests. Hence, the anti-cancer potential of probiotics must be proven *in vivo* models and continue towards animal and clinical trials.

L. acidophilus is known to prolong the initiation of colon tumors. It was established that feeding milk and colostrum fermented with *L. acidophilus* lead to in 16–41 % decrease in tumor proliferation [134].

The other probiotic *L. bulgaricus* has also been reported to induce anti-tumor activity against sarcoma-180 and solid Ehrlich ascites tumors [135]. The mechanisms by which probiotics apply anti-tumor activity are

1) Varying the immune functions associated with immune response
2) Anti- proliferative effects *via* regulation of apoptosis and cell differentiation.
3) Suppressing the production of enzymes like β-glucuronidase, urease, choloylglycine hydrolase, azedoreductase and nitro-reductase by bad bacteria especially entero-pathogens such as *E. coli and Clostridium perfringens*.

Beta-glucosidase and urease alter pro-carcinogens in to adjacent carcinogens. *Propionibacterium freudenreichii* was shown to encourage cell death of human colon and gastric cancer cell lines through secretion of SCFAs in to culture media [135].

Bifidobacteria probiotics reduced colon carcinogenesis induced by 1, 2-dimethylhydrazine in mice when used with FOS and repressed liver and mammary tumors in rats [136]. GOS consumption in humans resulted in abridged activity of nitro reductase which is complicated in producing genotoxic metabolites, indicating the potential of prebiotics and probiotics to Dietary administration of *B. longum* and oligofructose and inulin inhibits the formation of pre-neoplastic lesions. In addition, *B. longum* suppressed mammary and colon cancer [137].

Lactic acid bacteria and *Bifidobacteria* are the most common types of microbes used as probiotics, although certain yeasts and bacilli may also be helpful to the host. The immunomodulatory effect of probiotic bacteria was claimed by Metchnikoff over 100 years ago [138]. There has been an enlarged interest in the scientific com- munity on the protecting roles of probiotics on intestinal diseases, especially colon carcinogenesis. Orlando *et al.* [139] found that *Lactobacillus* GG administration induced a significant reduction in polyamine biosynthesis in both the HGC-27 and DLD-1 cancer cell lines. Kim *et al.* [140] assessed the anticancer activity and bacterial enzyme inhibition of *B. adolescentis* SPM0212. The strain repressed the proliferation of three human colon cancer cell lines: HT-29, SW 480, and CaCo2 and also dose-dependently repressed TNF-α production and changes in cellular morphology. Urbanska *et al.* [141] studied the assets of microencapsulated probiotic bacterial cells in a yogurt formulation in MIN mice carrying a germline APC mutation. Daily oral administration of the microencapsulated *L. acidophilus* resulted unimportant destruction of colon tumor incidence, tumor-multiplicity, and reduced tumor size. Certain strains of lactic acid bacteria have been found to prevent putative preneoplastic lesions or tumors induced by carcinogens.

Goldin *et al.* [142] showed that a exact strain of *L. casei* subsp. *rhamnosus* chosen GG can hinder with the initiation or early promotional stages of DMH-induced intestinal tumorigenesis. Consumption of large quantities of dairy products such as yogurt and fermented milk comprising *Lactobacillus* or *Bifidobacterium* may be related to a lower incidence of colon cancer [143]. Ingesting of lactobacilli by volunteers has been shown to reduce the mutagenicity of urine and feces associated with the ingestion of carcinogens in cooked meat [144]. It is possible that the *L. acidophilus* supplements are influencing excretion of mutagens by simply compulsory them in the intestine. Though, lactic acid bacteria have also been shown to disturb the host. Mucosal cell proliferative activity in upper colonic crypts of patients with colon adenomas significantly reduced after the administration of *L. acidophilus* and *B. bifidus* cultures [145].

Probiotic bacterium is shown to advance proliferation of immune cells [146] and swift production of pro-

inflammatory cytokines, such as tumor necrosis factor and interleukin 6 [147]. In comparison, probiotic bacteria intermediate suppression of lymphocyte propagation and cytokine produced by T cells [148]. One study group tried to comparation the antiproliferative outcome of several probiotic bacterial strains in their nonviable systems [149]. The probiotic strains were cultivated. When the rate of proliferation was compared among cultures containing an indistinguishable protein concentration, a grading of immunomodulation between probiotics was shown. They showed that particular probiotic bacteria possess important anti-inflammatory properties similar to a therapeutic pharmaceutical agent.

Lactic acid bacteria or a soluble compound formed by the bacteria may interact straight with tumor cells in culture and inhibit their growth. Lactic acid bacteria significantly reduced the growth and viability of the human colon cancer cell line HT-29 in culture, with a significant increase in dipeptidyl peptidase IV and brush border enzymes, suggesting that these cells might have entered a differentiation process. Milk fermented by *B. infantis*, *B. bifidum*, *B. animalis*, *L. acidophilus* and *L. paracasei* inhibited the growth of the MCF7 breast cancer cell line, the antiproliferative effect not being related to the presence of bacteria. These findings suggest the presence of an ex novo soluble compound produced by lactic acid bacteria during milk fermentation or the microbial transformation of some milk components in a biologically active form [96].

Total, studies *in vitro* systems and in an widespread range of animal representations afford considerable sign that probiotics, prebiotics and symbiotics use good properties. [136].

3.6 Effective Dosage of Probiotics for Cancer Therapy

Little is known about the ideal amount of live probiotic bacteria to be managed [150]; this amount is not easy to regulate: it is strain-specific, and it possibly depends on the type of advantage sought for with the management of probiotics (different functional effects may require different amounts of live probiotics). Of course, the overall sum cannot be low, if the aim is to distinctly influence the composition of the microbiota of the host. It must be highlighted that, in cases of microbial associations, each species in "competition" with a useful action must be if in appropriate ate quantities. In the nonappearance of exact dose-response studies, however, some facts stated in the AFSSA paper (AFFSA, 2005) are value reiterating: (1) "The dose of probiotics consumed is an important factor to get high concentrations in the several compartments of the gastrointestinal tract." "It is often said that probiotic concentrations must be greater than or equal to 106 CFU/mL in the small intestine (ileum) and 108 CFU/g in the colon, but the methodical basis for these statements is relatively weak." "The concentrations in the colon have been anticipated because they resemble to less than 1/1000 of the autochthonous microbiota present (which it could be reasonably expected has more chance of being active than microbiota present at even lower levels)." Sivieri *et al.* [151] directed a placebo-controlled design trial involving 30 male Wistar SPF rats to evaluate the properties of a probiotic strain, *Enterococcus faecium* CRL 183 on the occurrence of colorectal tumors induced by 1,2-dimethlhydrazine (DMH). The authors described that rats administered with *E. faecium* CRL 183(108 CFU/ml) for 24 weeks showed a 40% decrease of adenocarcinoma incidence and diminished mean tumor volumes related to rats without the administration of probiotics. Singh *et al.* [152] showed a placebo-controlled design trial to measure the effects of *B. longum* on 60 male F344 azoxymethane (AOM)-induced colon carcinogenesis rats. The rats were fed a altered AIN-76A diet containing 0% or 2% lyophilized cultures of *B. longum* (4 × 1010 live cells/g diet) and absorbed AOM dissolved in normal saline, once weekly for 2 weeks and killed on 40 weeks after second AOM injection to assess the incidences of colon tumor. The authors revealed that the administration of *B. longum* evocatively reduced the prevalence of colon adenocarcinomas, colon tumor multiplicity in terms of tumors/animal, and tumors/tumor- bearing animal linked to those on the control diet. Lidbeck *et al.* (1991) deliberate the effect of *L. acidophilus*-fermented milk on fecal microbiota and β-glucuronidase activity in 14 colon cancer patients. The authors defined that the feeding of *L. acidophilus* (1011 CFU/day) for 6 weeks caused a droplet of *Escherichia coli* and increased the number of lactobacilli in the feces that later led to a 14% reduction of β-glucuronidase activity, an enzyme which makes carcinogens in the digestive system of humans. It was supported by Ling et al. [153] that studied the effect of *Lactobacillus* strain GG on the fecal enzyme activity in 64 subjects. The authors initiate that the ingesting of yogurt containing viable *Lactobacillus* strain GG (1011 CFU/L) reduced not only fecal β-glucuronidase but also other fecal enzyme activities such as nitro reductase and glycocholic acid hydrolase activities ($P < 0.05$) after consumption of yogurt containing probiotic for 4 weeks. Same observation was reported by Marteau *et al.* [154] that the nitro-reductase activity was significantly reduced ($P < 0.05$) in nine healthy

volunteers after administration of 100 g/day of fermented milk product containing *L. acidophilus* (107 CFU/g), *Bifidobacterium bifidum* (108 CFU/g), *Streptoccoccus* (*Lactococcus*) *lactis* (108 CFU/g), and *Streptoccoccus cremoris* (*Lactococcuslactis* subsp. *cremoris*) *lactis* (108 CFU/g) for 3 weeks. The authors also found that the β-glucosidase activity was suggestively increased ($P < 0.05$) after the feeding of probiotic fermented milk. In alternative study, Goldin and Gorbach [155] assessed the properties of milk containing *L. acidophilus* on fecal enzyme activity in 16 women and 5 men. The authors found that the oral management of *L. acidophilus* (2 × 106 CFU/ml) for 4 weeks meaningfully reduced ($P < 0.05$) most of the fecal enzyme doings such as β-glucuronidase, nitroreductase, and azoreductase with two to four-fold reductions during the period of lactobacilli feeding.

3.7 Use of Probiotics in Oncology

As considered overhead, chemotherapy, targeted therapy, immunotherapy and radiotherapy characterize the pillars of the presently available anti-cancer treatments. Such actions may cause diverse and even radical side effects in patients [156]. Frequent preclinical studies and clinical trials share the collective goal of appraising the overall usefulness of probiotics in reducing the risk and the harshness of such anti-cancer treatments related-toxicity, mainly diarrhea and mucositis [157]. In fact, the aim of managing probiotics to cancer patients, principally Lactobacilli, is to re-populate the approved patients' gut microbiota, thus re-establishing the levels and functionality of the commensal bacteria, fatigued after the treatments [158]. Although probiotics are frequently regarded as safe, the main concerns of handling them to immunocompromised cancer patients are both the potential risk of opportunistic infection growth and the transmission of antibiotics resistance [159]. Contempt of that, probiotics management in multiple trials has shown helpful effects on ameliorating diarrhea and other gut-related damages following anti-cancer therapy, thus re-establishing a healthy intestinal microbiota configuration [160] Moreover, within the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) and European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for Gastrointestinal Mucositis, probiotics containing Lactobacillus species are optional be used to avert diarrhea in patients getting chemotherapy and/or radiation therapy for a pelvic malignancy (Level of evidence III) [161].

Assumed that a growing body of studies authenticated the vital role of microbiome in cancer, numerous clinical studies are now ongoing with the mutual aim of study the sustaining latent of deploying gut microbiota in cancer patients. Consequences from early clinical trials are auspicious. In 2010, it was assessed for the first time the communication between probiotic administration, discrepancy of gut microbiota configuration, and regulation of intestinal immune-functions in cancer patients experiencing colorectal resection [162]. A mixture of two probiotic bacterium species Bifidobacterium longum (BB536) and Lactobacillus johnsonii (La1) was directed to the patients in the double-blind study, result that one of that, La1, was able to stick to to the colonic mucosa, thereby reducing the concentration of gut pathogens and moderating the local immunity [162]. Subsequently, in 2014, a randomized double-blind controlled trial assessed the valuable administration of the probiotics Bifilact (*Lactobacillus acidophilus* LAC361 and Bifidobacterium longum BB536) on significantly reducing moderate and severe treatment-induced diarrhea during pelvic radiation [163].

On the same line, in 2015, for the primary time, a clinical trial appraised the probiotic formula Colon Dophilus (mixture of 10 different probiotic strains) in the inhibition of diarrhea in patients with metastatic CRC, treated with irinotecan-based chemotherapy, suggesting that the administration of such probiotics is harmless and leads to a reduction in the occurrence and severity of diarrhea and chemotherapy persuaded gastrointestinal toxicity [164]. In 2016, another double-blind, randomized trial established that the administration of a combination of prebiotics and probiotics to patients endangered to CRC resection may alleviate irritable bowel syndrome (IBS), often succeeding the operation [165] In the same year, another trial further examined the effects of randomized oral administration of the probiotic *Saccaromices bulardii* in CRC patients. They initiate that this probiotic was able to downregulate pro-inflammatory cytokines in treated patients, though with lacking effects on the post-operative contagion rates [166]. Moreover, bestowing to the result of a trial published in 2017, the randomized direction of Bifidobacterium lactis and Lactobacillus acidophilus to CRC patients, can alteration the epigenetic patterns of tumor tissue from its baseline, with possible therapeutic benefits in CRC by management of the gut microbiota [167]. The same year a randomized clinical trial with CRC patients demonstrated that the perioperative management of a mixture of prebiotics and probiotics, meaningfully reduced postoperative infection rates in patients with CRC [168].

Irrespective the observed valuable effects, larger and skillful clinical trials are further desired to truly endorse both the efficacy and the safety of

administering selected species of probiotics during or following anti-cancer treatment. *Usage of Fecal Microbiota Transplantation (FMT) in Oncology*. The exchange of gut microbiota among individuals has been cast-off to cure pathogens infections or in the behavior of gut inflammatory disease and dysbiosis. For example, FMT has been used to cure recurrent *Clostridium difficile* duodenal infection [169]. Moreover, FMT has been used in a Graft Versus Host Disease (GVHD) after allogeneic stem cell relocation [170]. Regarding anti-tumor therapeutic applications, preclinical studies done in mice established the efficacy of FMT in reducing colon tumorigenesis, though the effectiveness in clinical trials still needs to be additional proven ([171]. Numerous clinical trials, considered to assess the use of FMT in cancer patients are presently ongoing, with the common goal of averting and/or ameliorating duodenal side-effects of anti-cancer therapies in cancer patients .

Despite the success of FMT, there is still an absenteeism of regulator in this procedure since the whole gut microbiota is moved along with the satisfying bacteria species. Consequently, it is of key position the vigilant control of the donors' health and their gut microbiome specific conformation [172].

3.8 Anti-carcinogenic Mechanisms of Probiotics on GI Cancers

Tentatively, probiotics are able to decrease cancer risk by several mechanisms. Oral administration of probiotics has numerous effects such as standardization of gut microbiota, development of the gastrointestinal barrier, hang-up of potential pathogens, anti- inflammatory activities and conquest of tumor formation and growth. Probiotics have abundant anticancer assistances and have a main influence on the quantitative and/or qualitative changes of the intestinal microbiota. The intestinal microbiota has been related to GI cancer growth also by production of toxic and genotoxic bacterial metabolites that can lead to mutations by requisite specific cell surface receptors and affecting intracellular signal transduction. Definite strains of bacteria are involved in the pathogenesis of cancer, counting *Streptococcus bovis*, *Bacteroides*, *clostridia*, and *H. pylori* [173]. On the different, some bacterial strains, with L. acidophilus and B. longum, inhibit carcinogenic tumor growth in the colon [174]. Thus, a equilibrium between "detrimental" and "beneficial" bacteria has insinuations in setting the stage for cancer Everchanging the proportion of microbes has been reported to influence carcinogen bioactivation and thus cancer risk. It is progressively apparent that dietary components can significantly adapt this balance. In addition, probiotic bacterium also disturb the intestinal microbiological compositions, thus absolutely affect the host by improving intestinal barrier integrity, inhibiting growth of pathogens, dropping metabolism of pro-carcinogenic substances. The aids of probiotics are not only incomplete to the prevention and hang-up of carcinogenic agents, but they can also comprise the therapeutic effect and the preclusion of cancer treatment complications. The therapeutic effect of probiotics can be due to the manufacture of antimicrobial compounds such as bacteriocins and antibiotics. Bacteriocins produced by LAB are peptides or small proteins that are regularly inhibitory to many undesirable bacteria, including food-borne pathogens [175]. It has also been suggested that LAB or a solvable compound produced by the bacteria may relate with tumor cells in culture and prevent their growth. The competitive behavior of probiotics with pathogens is related to bond to epithelial cells [176]. Several studies that categorized LAB from dissimilar origins has shown that the capability to stick to to epithelial cells is strain dependent [177]. The oppressive effect of probiotics was also related with erection of short chain fatty acids (SCFAs), which might be replicated, by the enhancement of SCFAs-related pathway [178]. Chronic inflammation has been acquainted as a danger factor of cancer [179]. For example; inflammatory bowel disease (IBD) is a menace factor of colon cancer and the risk of HCC can be amplified by inflammatory circumstances, such as hepatitis B, C virus infection [180]. Irritation not only plays a role in colitis-associated colon cancer, but may also occur in sporadic colon cancer and disturb the development of cancer ([181]. *L. rhamnosus* GG was testified to avert colon carcinogenesis, ushered by the destruction of NFkB pathway [182], a pro-inflammatory pathway that relates IBD and colon cancer [183].

3.9 Risk Factors

Most ecological hazard factors are hesitantly controllable to some level by evading high risk factors and augmenting protective factors as much as possible. Chief preventable risk factors include: tobacco, betel quid and chewing tobacco, diet, infection, occupation, alcohol, sunlight, radiation, pollution, medicine and medical procedures, industrial products, food additives, reproductive factors, sexual behavior, obesity, exercise (sedentary workers), and stress. Nourishment plays an important role in the etiology of cancer, but its relation to cancer is complicated. Extra intake of some food components such as fat, calorie, and salt and insufficient intake of some other food components such as dietary fiber, fresh vegetables, and fruits elevate risks of cancer of the esophagus, stomach, colon-rectum, breast, and

some other sites. It is significant to avoid excess intake of fat, calories, and salt. However, it is not easy to change dietary habits and food processing methods. Thus, diet will also persist a main risk factor of cancer in the twenty-first century. Approximately dietary factors can take a role in cancer deterrence and/or treatment. For instance, probiotics, as feasible microorganisms, have been recommended to have a serious role in setting the tone for a strong bowel, counting the risk for emergent cancer

4. THE IMPORTANCE OF PROBIOTICS IN THE PREVENTION AND TREATMENT OF CANCER TUMORS

A study led by Marteau et al. showed that reduced levels of nitro-reductase later a three-week period of ingesting of lactic fermented products comprising *Lactobacillus acidophillus, Bifidobacterium bifidum, and mesophilic Streptococcus lactis and Streptococcus cremoris* cultures did not change the activity of beta–gluonidase and azoreductase. This shows that the capability to modulate the activity of bacterial enzymes is dependent on the probiotic strain [184].

It was also observed that the administration of Bifidobacterium breve Yakult to patients during chemotherapy defends them in contradiction of contagions and alteration of the intestinal ecosystem [185].

In alternative study with 206 radiotherapy patients, the management *of Lactobacillus rhamnosus* eased gastrointestinal toxicity associated with radiation [186].

The administration of Lactobacillus acidophilus and *Bifidobacterium bifidum* also resulted in an important development in stool consistency, a decrease in radiotherapy-induced diarrhea, and abridged the need for anti-polar agents. (Chitapanarux *et al*, 2012)

Research linked to the effect of probiotic bacteria on cancer cells, and also to animals with induced cancer or having directed carcinogens, is presented in Table given below. These results show that probiotics have anti-cancer properties.

5. RESEARCH ON CELL LINES/*In vitro*

5.1 Probiotics and Operations

Clinical studies have shown that some probiotic strains can be helpful in controlling postoperative inflammatory conditions.*Lactobacillus johnsoni La1*, administered orally before and after the treatment, adheres to the intestinal mucosa, reducing the number of potentially pathogenic bacteria in the faeces (enterobacteria and enetorococci) and modulating local immunity [162]. Fermented dairy products, which have been suggested as products affecting the human body, protect against the occurrence of colorectal cancer.Studies on humans related to the use of probiotics for prophylaxis, as well as in the treatment of colorectal cancer, have been included in Table given below. It has been shown, among other things, that perioperative administration of probiotics effectively reduces post-operative infectious complications.

Table 6. The impact of probiotic bacteria on cancer cell lines with induced colorectal cancer.

Probiotic Bacteria	Cell Lines	Effects/Mechanisms	Source
Lactobacillus rhamnosus GG	Caco–2	Decreased level of IL–8.	[187]
Lactobacillus casei ATCC393	CT26 (murine colon carcinoma cell lines); HT29 (human colon carcinoma cell lines) Administration of live L. casei and bacterial components to cell lines.	Anti-proliferative activity. Live L. casei induced apoptotic death of CT26 and HT29 cells.	[188]
40 different probiotic bacteria isolates	Caco–2, HRT–18 Vero cells Using Trypan Blue assays (TBE) and 3–(4, 5–dimethylthiazolyl–2)–2, 5–diphenyltetrazolium bromide (MTT)	Two isolates of Lactobacillus acidophilus LA102 and Lactobacillus casei LC232 showed clear cytotoxic activity. They showed no cytotoxic activity on normal Vero cells.	[189]

6. RESEARCH ON HUMAN PREVENTION

Table 7. The results of the impact of probiotic bacteria in the prevention and in the treatment of colon cancer

Probiotic Bacteria	Subjects	Effects/Mechanisms	Source
Lactobacillus rhamnosus LC705 and *Propionibacterium freudenreichii* ssp. shermanii JS	38 men (between 24 and 55 years old).	Decreased beta-glucosidase activity (by 10%) and urease (by 13%). Increasing the fecal amount of bacteria of the genus Lactobacillus and propionibacteria.	[190]
Lactobacillus gasseri OLL2716 (LG21)	10 people with colorectal cancer and 20 healthy patients	Increasing the number of bacteria from the genus Lactobacillus, synthesis of isobutyric acid, NK cell activity. Reducing the amount of *Clostridium perfringens*.	[191]
Streptococcus thermophilus and *Lactobacillus delbruckii* sub sp. *Bulgaricus*	45 241 healthy people (14 178 men, 31 063 women)	Reduction in the risk of colorectal cancer correlated with increased consumption of yogurt (especially in men).	[192]

Treatment

Probiotic Bacteria	Subjects	Effects/Mechanisms	Source
Bifidobacterium longum	60 patients with colorectal cancer undergoing colon resection	Increasing the amount of bacteria of the genus Bifidobacterium, and reducing the amount of bacteria of the genus Escherichia ratio of these bacteria was different to the pre-operative.	[193]
Bifidobacterium breve strain Yakult	42 patients during chemotherapy (19 people were in the study group, 23 in the control group)	Reduction in the incidence of fever and the use of intravenous antibiotics was lower in the study group than in the control group.	[194]
Lactobacillus acidophilus, L. plantarum, Bifidobacterium lactis and *Saccharomyces boulardii*	164 patients with colorectal cancer undergoing colorectal surgery	Significantly decreased the risk of postoperative complications. In the probiotic group, a positive correlation was observed between the expression of the SOCS3 gene and the expression of the TNF gene and circulating IL–6.	[195]

Treatment

The common ways for treatment or control of tumor consist of medical and nutritional management. Medical approaches that are mutual in cancer therapy or control are surgery, radiation-therapy, chemotherapy, biotherapy, and hematopoietic cell replacement. Consumption behaviors play a very significant role in health promotion and disease prevention. Chemoprevention includes specific compounds or drugs used to avert, delay, or retard the growth of cancer [196]. One of the important nutritional compounds that has a significant role in tumor action and/or control is probiotics, live microorganismisms, that, when achieved in satisfactory amounts, thoughtful a health benefit on the host.

Table 8. Commercial probiotic dairy products

Type of product	Trade name	Probiotic microorganism
Fermented milk with high viscosity	Bifisoft, Bifidus, Bioghurt, Biofit, BiofardePlus, Biola, Biologic bifidus, Cultura Dofilus, Dujat Bio Aktiv, Ekologisk Jordgubbs Yoghurt, Fit&Aktiv, Fjäll Yoghurt, Gaio Dofilus, Gefilac, Gefilus, LC 1, Probiotisches Joghurt, ProViva, RELA, Verum, Vifit Vitamel, Vitality, Weight Watchers, Yogosan Milbona	*L. acidophilus*, *L. acidophilus* LA5, *L. rhamnosus* (LGG, LB21 and 271), *L. casei*, *L. casei* L19, *L. johnsonii*, *L. plantarum* 299v, *L. reuteri*, *Lactococcus lactis* ssp. *lactis* L1A, *B. bifidum*, *B. animalis* ssp. *lactis* BB-12, *B. animalis* ssp. *animalis*
Fermented milk with low viscosity (*e.g.* cultured buttermilk, yoghurt drink, dairy drink)	A-fil, Actimel, Aktifit, AB-piimä, Bella Vita, Bifidus, Biofit, Biola, Casilus, Cultura, Emmifit, Everybody, Fit&Aktiv, Fundo, Gaio, Gefilac, Kaiku Actif, LC 1 Go!, LGG+, Onaka, Öresundsfil, Philura, Probiotic drink, ProViva, Pro X, Verum, ViktVäktarna, Vitality, Le'Vive+, Yakult, Yoco Acti-Vit	*L. acidophilus*, *L. acidophilus* LA5, *L. casei* (F19, 431, Imunitas, Shirota), *L. rhamnosus* (LGG, LB21 and 271), *L. johnsonii*, *L. plantarum* 299v, *L. reuteri*, *L. fortis*, *Lactococcus lactis* ssp. *lactis* L1A, *B. bifidum*, *B. animalis* ssp. *lactis* BB-12, *B. animalis* ssp. *animalis*, *B. longum* BB536
Non-fermented dairy products (*e.g.* milk, ice cream)	Gefilus, God Hälsa, RELA, Vivi Vivo	*L. rhamnosus* LGG, *L. plantarum* 299v, *L. reuteri*

6. CONCLUSION

This review supports the effectiveness of probiotics in cancer prevention and control by numerous mechanisms for instance stimulating the immune system, reducing the incidence of infections, regulating gut inflammation, and binding toxic compounds. They also depend up on the diet intake, conferring to numerous human and animal studies, several of the specific probiotic bacteria and their metabolites have valuable effects in cancer control and/or anticipation. Consumption of *Lactobacillus* or *Bifidobacterium* in dosage of 10^{10}-10^{11}cfu per day for at minimum 5 – 7 weeks may lesser occurrence of cancer; though, more studies are needed to examine the dealings between probiotics, diet, and cancer risk.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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