Benefits of using probiotics as adjuvants in anticancer therapy (Review)

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Abstract. Cancer is the second leading cause of mortality worldwide and the constant search for novel therapeutics aims to increase the overall survival of the affected population. The human microbiota evolves with the host throughout the course of its entire life, as a direct consequence of individual diet and lifestyle habits. The gut microbiota tremendously affects human homeostasis and it has been widely observed that maintaining a healthy gut may prevent diseases, as well as ameliorate pathological conditions. According to the World Health Organization, probiotics may confer a health benefit on the host when administered in adequate amounts. Anticancer therapy often causes severe side-effects, including gastrointestinal toxicity. Several clinical trials have highlighted the efficacy of administering probiotics to cancer patients receiving anticancer care, with proven efficacy in reducing gut-related and life-threatening side-effects. To corroborate the clinical results, recent translational studies have indicated that the specific administration of selected bacterial gut species are capable of improving the immune check-point immunotherapy clinical outcome. *Lactobacillus rhamnosus* GG (LGG), a model probiotic widely studied in oncology, has been proven to be beneficial when administered during anticancer therapy. In this review, we report the up-to-date clinical advancements obtained following the administration of probiotics during anticancer therapy, with particular focus on the promising probiotic strain LGG.

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Contents

1. Introduction

Every exposed human body surface, including the skin, genitourinary, gastrointestinal and respiratory tracts, are heavily colonized by as many as 10-100 trillion microorganisms, including bacteria, fungi, archaea and viruses (1). In the recent years, commensal microorganisms have been identified as key determinants of a host's homeostasis and health (2). In particular, among the human symbiotic microbial populations, the gut microbiota is the most extensively populated, hosting up to 70% of the microbes inhabiting the whole body (3). Gut microbiota is the name given to the heterogeneous population of commensal microorganisms, inhabiting the gastrointestinal tract, mostly the large intestine. This population constitutes an agent to which we are constantly exposed, at high doses, throughout an entire lifespan (4). The human gut is populated by 1,000 different bacterial species, prevalently belonging to the phyla of Firmicutes and Bacteroidetes (5).

The intestine is the interface between the gut commensal microbiota and the human body (6). On the one hand, the gastrointestinal enteroendocrine cells secrete over 30 different peptide hormones involved in key functions, including gastrointestinal motility, food digestion and neuromodulation (7). It has been demonstrated that gut-secreted hormones are able to modify the gut microbiome composition, as during the response to stress (8-10). On the other hand, the gut microbial population produces or transforms active molecules, which may be sensed by the gastrointestinal cells of the host (8). The derived functional effects range from the modulation of the host's metabolism to the maintenance of gut barrier integrity, xenobiotics metabolism, protection against gastrointestinal pathogens and modulation of the host's immune system (11-14). Notably, certain commensal bacteria produce

essential micronutrients, including vitamin K and vitamin B. Additionally, a number of gut commensals can transform amino acids into signaling molecules, as for example glutamate into gamma-amino butyric acid (GABA) or histidine to histamine. Finally, several Bacteroidetes are able to catabolize phenolic compounds, as well as secondary bile acids, moreover to synthetize the anti-diabetics linoleic acid (15). Another class of hormone-like metabolites produced by the human gut commensals is represented by the short chain fatty acids (SCFAs), derived from the bacterial fermentation of dietary fibers (16). The SCFAs, once synthetized in the intestine, are transported to the liver where they are utilized as a key source of energy. Additionally, SCFAs play a role in controlling glucose and the lipid metabolism by affecting the gut epithelial hormone peptide secretion (17).

Given the reported functional crosstalk between the gastrointestinal microbiota and its host, the preservation of the equilibrium in both composition and the relative abundance of the gut microbial population is fundamental for the correct fulfilment of pivotal host's metabolic, as well as immune functions (18-20). Any disequilibrium in this delicate balance may lead to a defective microbiota, a condition known as dysbiosis, mostly linked to several human pathologies, including cancer (21).

The gut microbiome is defined as the whole genome of the host's gut microbiota, and it encodes 100-fold more genes than the human genome (22). Over the past 10 years, classical fecal-derived microbe cultivation studies have been strongly integrated with metagenomics approaches, combining next-generation sequencing (NGS) with the computational analysis of the 16S rRNA amplicons. Progresses in metagenomics studies, together with many advancements in transcriptomics and metabolomics, have allowed the characterization of both a diversity and abundance of the gut microbiome, with the final goal of determining the impact of each individual gut-populating species on the health of the host (23,24). These novel approaches are depicting the deep impact of the microbiome diversity and composition on human health, as disclosed by the Human Microbiome Project and the large number of originating publications (25-28).

A healthy gut microbiome is defined by a functional core of metabolic and other molecular functions, which are not necessarily performed by the same bacterial species in each different individual (29). The term 'probiotic' means pro-life. Probiotics are currently defined by the Food and Agriculture Organization of the United Nations and by the World Health Organization (FAO/WHO) as 'live microorganisms, which, when consumed in adequate amounts, confer a health effect on the host' (30). They are highly present in fermented food and yoghurt. The vast majority of these probiotics are lactic-acid producing, non-pathogenic bacteria, such as *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Propionibacterium* and *Enterococcus* or non-pathogenic yeasts including *Saccharomyces boulardii* (30). Probiotics are administered orally and arrive alive in the intestine (30). They are often administered in combination with specific prebiotics (undigestible food specifically metabolized by probiotics), to form synbiotic mixes (31). Health benefits derived from administering probiotics to healthy individuals include improved digestion, immune defense mechanisms and nutrient absorption. Importantly, probiotics have been proven to be able to revert intestinal dysbiosis, which may play a role in the development of several degenerative diseases, as well as chronic diseases, including cancer (32).

A growing amount of clinical studies are currently investigating the impact of probiotics on the treatment of intestinal toxicity during chemotherapy, immunotherapy and radiation, generating promising results. The present review aimed to summarize the up-to-date clinical observations concerning the role played by probiotics administered in association with anticancer therapy.

2. Gut microbiota and cancer

The gut microbiota can be considered a factor to which we are exposed throughout an entire lifespan, whereas intestinal dysbiosis has been found to be linked to the tumorigenesis of both local gastro-intestinal cancers and tumors localized in distant sites of the body (33). Both environmental exposure (e.g., to cancerogenic substances or UV radiation) and lifestyle habits significantly influence individual cancer risk (34-37). This risk is associated with the dose, duration and the combination of these exposures among each other, also depending on the individual genetic background (38-43). In fact, neoplasms bear an intrinsic complexity, as they are derived from the stochastic acquisition of driver mutations within genes involved in key processes (including DNA duplication, DNA repair and oxidative stress response). Thanks to the accumulation of mutations over time and space, cancerogenic cells adapt to the hosting organism, therefore transforming from a normal cell into a malignant one (44-47). Moreover, given the stochastic gathering of mutations, together with the intrinsic tumor cellular genomic instability, epigenetics (including altered DNA methylation, as well as miRNA imbalance), transcriptional and post-transcriptional intracellular changes, from one original cancer can lead to the development of a molecularly varied bulk tumor, made of multiple cancer cell clones, each one presenting a differential sensitivity to the anticancer therapies (48-60).

Anticancer therapies are designed with the final goal of being effective in the eradication of the targeted malignancy. As almost every available treatment is toxic towards normal cells, their use may be coupled with toxic side-effects, some of which can compromise the overall survival of the patients (61). Importantly, the intra-tumoral variety is tightly linked to the development of the resistance to therapy, considered the first cause of failure of the available treatments, as well as subsequent tumor relapses (62). To fight the resistance, integrated therapies and personalized approaches, based on the specific genetic features of the malignancy, are in constant development (62).

The host's immune system plays a fundamental role in fighting and eliminating tumor cells (63-65). On their side, malignant cells, thanks to their genetic instability, constantly develop novel strategies with which to escape from immunosurveillance (63,66). Targeted immunotherapy represents a novel anticancer approach, able to boost the host anti-tumor immune response, and, at the same time, help to 'hit' cancer resistance and recurrence mechanisms (67,68).

Taken together, radiotherapy, chemotherapy and immunotherapy, given their general toxicity, can compromise the gut

microbiome of patients. At the same time, modulating the gut microbiome composition may deeply influence the outcome of patients to therapies (69). It is therefore of utmost importance to develop novel strategies with which to manipulate the gut microbiome, with the main goal of improving the therapeutic outcome of patients, without any associated risk (70,71).

3. Gut microbiota and anticancer therapy

A dysbiotic gut microbiota deeply influences both cancer pathogenesis and its therapeutic outcome, with the latter tightly connected with the ability of the gut microbiota to metabolize antitumoral compounds, as well as to modulate a host's immune response and inflammation pathways (72). The combination of these two effects explains the strong involvement of the patients' microbiome composition in affecting their final outcome to treatments (73).

As regards the effects of the gut microbiome on the host's immune system, the past year witnessed the publication of marking breakthrough, strongly coupling the patients' microbiome composition with the efficacy of immune checkpoint inhibitors-based immunotherapy (74-76). Immune checkpoint inhibition consists of the administration of therapeutic agents able to block the immune-inhibitory pathway, thus modulating T cell activation against tumor target cells [i.e., monoclonal antibodies blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein 1 (PD1) or programmed death-ligand 1 (PD-L1) targets] (77,78).

In particular, Routy *et al* (74) observed that patients with melanoma treated with antibiotics along with the anti-PD1/anti-PD-L1 immunotherapy had a lower survival rate. Following the metagenomic fecal analysis, anti-PD1 responders were found enriched in two phyla (*Akkermansia* and *Alistipes*). Performing Fecal Microbiota Transplantation (FMT) from patients to germ-free mice, the authors found that *Akkermansia muciniphila* increased intra-tumoral cytotoxic T cell infiltrates, thus ameliorating the PD-1 blockade response in mice (74). Similarly, Gopalakrishnan *et al* (75) carried out the metagenomic analysis on stool samples from patients with melanoma, finding that the anti-PD1 responders' microbiome differed in composition compared with that of non-responders. In fact, there was an increase in the abundance of Clostridiales, Ruminococcaceae and Faecalibacteriae. Functional studies performed with FMT in germ-free mice have further demonstrated how the treatment of mice with the identified bacteria, along with the anti-PD1 therapy, significantly reduced the growth of melanoma (75). Likewise, Matson *et al* (76), accomplishing the metagenomic analysis of fecal samples from patients with melanoma treated with immune checkpoint inhibitors, found that responders had a different microbiome profile compared to not responders. They identified and functionally proved *in vivo* the role played by *Bifidobacterium longum*, *Enterococcus faecium* and *Collinsella aerofaciens* in ameliorating anti-PD-L1 efficacy (76).

Taken together, these results provide strong evidence of the pivotal role of selected gut resident strains in modulating the effects of both immunotherapy response and toxicity. Nevertheless, several obstacles still interfere with the robust translation of the described bench results to the bedside. In fact, the gastrointestinal microbiome of each single patient can be either detrimental or beneficial to tumor progression and therapy, depending on the prevailing inhabiting species. Moreover, the fact that often, cancer patients undergoing therapy are immunocompromised, has to be taken into careful consideration, as this delicate condition could lead to the development of defeating infections, due to the proliferation of opportunistic bacterial species. Consequently, it is necessary to carefully analyze both the risks and benefits of probiotics treatments coupled with anticancer therapy, with the final goal of pursuing only beneficial effects, without any safety issues.

4. Probiotics as adjuvants of anticancer therapy

Tremendous progress has been made over the past century to improve anti-cancer therapies, significantly reducing detrimental side-effects, with the final goal of improving the compliance of patients (79). Manipulating the intestinal microbiome through the oral delivery of probiotics is used to improve the safety, as well as to reduce the drastic gastrointestinal side-effects, which are often associated with anticancer treatments, mainly diarrhea and mucositis. In fact, probiotics have the great advantage of being inexpensive and are broadly regarded as safe (80,81). Generally, the use of probiotics in clinical practice has demonstrated that probiotics have a broad spectrum of benefits, including the amelioration of antibiotic- and *Clostridium difficile*-associated diarrhea, as well as respiratory tract infections (82). Repopulating the gut microbiota cancer of patients through the administration of probiotics, re-establishes both the abundance and the functionality of the commensal gut bacteria, which has been possibly depleted after the therapies (83). The main issues of administering probiotics to immunocompromised cancer patients are both the risk of opportunistic infections, as well as the potential transfer of antibiotics resistance (84,85). In spite of this, the administration of probiotics in multiple trials has shown the readjustment of a healthy intestinal microbiota composition, the amelioration of diarrhea and other types of therapy-associated damage to the gastrointestinal system, including mucositis (80). Moreover, probiotics containing the *Lactobacillus* species have been suggested as food supplements for the prevention of diarrhea and for the relief of mucositis in patients receiving chemotherapy and/or radiation therapy for a pelvic malignancy (86,87).

Fig. 1 summarizes both the benefits and the risks potentially associated with the administration of probiotics as adjuvants during anticancer therapy, highlighting how probiotics may modulate the delicate gut equilibrium, from a dysbiotic towards a healthy and functioning microbiota.

Following this perspective, a growing number of clinical studies are currently ongoing, with the common intent of investigating the therapeutic potential of gut microbiota manipulation in cancer patients through the oral administration of probiotics as food supplements, along with their anticancer treatment. The results from the published clinical trials are encouraging. In 2010, a double-blind clinical trial, performed on cancer patients undergoing colorectal resection, demonstrated the positive effects of probiotic administration on the gut microbiota composition, as well as on the regulation of intestinal immune functions (88). In particular, *Lactobacillus johnsonii*, administered to patients, was able to adhere to the

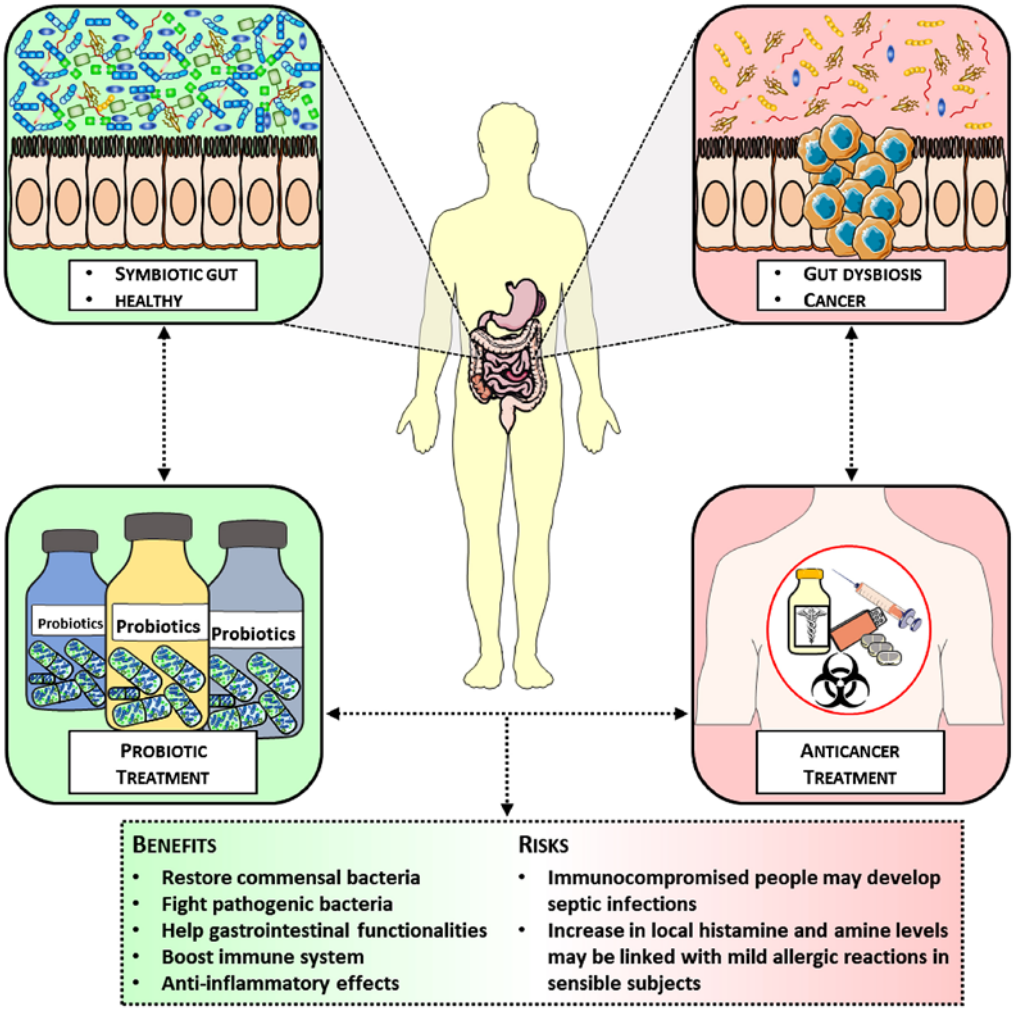

Figure 1. Benefits and risks of associating probiotics with antitumor therapy. Schematic representation of human healthy gut microbiota, populated by symbiotic bacteria (top left square) versus human gut microbiota affected by tumor condition and gut dysbiosis (top right square). Anticancer therapies may negatively affect gut microbiota thus generating a dysbiotic unbalance (bottom right square). Probiotic-based treatments may counterbalance dysbiotic conditions generated by tumor growth and anticancer therapy, with the effect of ameliorating detrimental gastrointestinal therapy-linked side effects, thus re-establishing intestinal symbiosis (bottom left square). The association of probiotics with anticancer therapy have benefits and risks (central bottom rectangle).

colonic mucosa, thereby reducing the concentration of gut pathogens and modulating the local immunity (88). In 2014, a double-blind controlled trial demonstrated the beneficial role of the probiotics *Lactobacillus acidophilus* and *Bifidobacterium longum* in reducing radiation-induced diarrhea, when administered to cancer patients receiving pelvic radiation therapy (89). Moreover, in 2015, a clinical trial evaluated the safety and efficacy of a probiotic formula consisting of 10 bacterial strains (including *Lactobacilli* and *Bifidobacteria*), orally administered along with irinotecan-based chemotherapy, to patients with colorectal cancer (CRC). The authors successfully found an effective reduction of diarrhea and gastrointestinal dysfunctions in patients receiving the probiotics (90). In 2016, another double-blind, randomized trial demonstrated that patients subjected to CRC resection exhibited a decreased risk of developing post-operatory irritable bowel syndrome (IBS), when co-treated with a synbiotic mix of prebiotics and probiotics (91). Also in 2016, another randomized trial performed in patients with colon-resected CRC came to the conclusion that *Saccaromices bulardii* effectively downregulated pro-inflammatory cytokines (92). In 2017, a randomized clinical trial demonstrated how the perioperative administration of a synbiotic mixture of probiotics and prebiotics significantly reduced post-operative infection rates in patients affected by CRC (93).

In addition to the described published findings, a number of clinical trials are currently ongoing to evaluate the safety and the efficacy of using probiotics with anticancer therapy. In fact, regardless the observed beneficial effects, it is of fundamental importance to truly establish the safety of administering probiotics to patients with severe cancer conditions in a larger cohort of cases. The complete list of the currently registered clinical studies (clinicaltrials.gov) untangling the effects of administering probiotics to cancer patients during their therapy, is reported in Table I.

5. LGG, a model probiotic for use as an anticancer adjuvant

The probiotic archetype *Lactobacillus rhamnosus* GG (LGG) represents one of the first studied bacteria in oncology (94). LGG is a gut-resident bacterium which has the ability to restore gut microbial balance, thanks to its anti-inflammatory properties (95-99). The benefits of administering LGG to cancer

Table I. Clinical studies registered at clinicaltrials.gov involving the use of probiotics in combination with anticancer therapy.

Study ID	Title of the study	Conditions	Interventions	Status	Ref.
NCT00936572	Probiotics In Colorectal Cancer Patients	CRC	Probiotics (*B. longum*, *L. johnsonii*)	C	(88)
NCT01839721	Impact of Probiotics BIFILACT® on Diarrhea in Cancer Patients Treated With Pelvic Radiation	CAN	BIFILACT (*L. acidophilus*, *B. longum*)	C	(89)
NCT01410955	Prevention of Irinotecan Induced Diarrhea by Probiotics	CRC	Colon Dophilus (*Lactobacillus* spp, *Bifidobacterium* spp)	C	(90)
NCT01479907	Synbiotics and Gastrointestinal Function Related Quality of Life After Colectomy for Cancer	CRC	Synbiotic Forte (*Lactobacillus* spp and prebiotics)	C	(91)
NCT01609660	Impact of Probiotics on the Intestinal Microbiota	CRC	*S. boulardii*	C	(92)
NCT01468779	Effect of Probiotics in Patients Undergoing Surgery for Periampullary Neoplasms	PC	Probiotic formula	C	(93)
NCT03420443	Action of Synbiotics on Irradiated GI Mucosa in CRC Treatment (FIPIREX)	CRC	Synbiotics	C	
NCT01723592	Orally Administered Probiotics to Improve the Quality of the Vaginal Flora of Women With Breast Cancer and Chemotherapy	BC	Probiotics (*Lactobacillus* spp)	C	
NCT02771470	Intestinal Microflora in Lung Cancer After Chemotherapy	LC	*C. butyricum*	C	
NCT01895530	Impact of Probiotics in Modulation of Intestinal Microbiota	CRC	*S. boulardii*	C	
NCT02021253	Influence of Probiotics Administration Before Liver Resection in Liver Disease	HC	Lactibiane (*B. lactis*, L. acidophilus, *L. plantarum*, *L. salivarius*)	C	
NCT03531606	The Effects of Mechnikov Probiotics on Symptom and Surgical Outcome	CRC	Probiotics	C	
NCT03782428	An Evaluation of Probiotic in the Clinical Course of Patients With Colorectal Cancer	CRC	HEXBIO (*L. acidophilus*, *L. lactis*, *L. casei*, *B. longum*, *B. bifidum*, *B. infantis*)	C	
NCT03358511	Engineering Gut Microbiome to Target Breast Cancer	BC	Primal Defense Ultra (*Lactobacillus* spp, *Bifidobacterium* spp)	O	
NCT03785938	Mucositis and Infection Reduction With Liquid Probiotics in Children With Cancer (MaCROS)	PEDC	Symprove (*L. rhamnosus*, *E. faecium*, *L. acidophilus*, *L. plantarum*)	O	
NCT02944617	Probiotic Yogurt Supplement in Reducing Diarrhea in Patients With Metastatic Kidney Cancer Being Treated With Vascular Endothelial Growth Factor-Tyrosine Kinase Inhibitor	RCC	Yogurt	O	
NCT03704727	The Effects of Probiotics on Intestinal Permeability in Gastrointestinal Cancer Patients in Chemotherapy	GIC	VSL3 (*Lactobacillus* spp, *Bifidobacterium* spp)	O	
NCT03742596	The Effect of Probiotics Supplementation on the Side Effects of Radiation Therapy Among Colorectal Cancer Patients	CRC	Probiotic Formula (*Lactobacillus* spp, *Bifidobacterium* spp)	O	
NCT03177681	The Effect of Yogurt in Cancer Patient With Moderate Gastrointestinal Symptoms	CAN	Yogurt	O	
NCT02351089	Probiotics in Radiation-treated Gynecologic Cancer (ProRad)	GYC	Probiotics	O	
NCT03705442	Probiotics as Adjuvant Therapy in the Treatment of Metastatic Colorectal Cancer (Probat-tmcc-17)	CRC	Omni-Biotic 10 (*Lactobacillus* spp, *Bifidobacterium* spp)	O	

Table I. Continued.

Study ID	Title of the study	Conditions	Interventions	Status	Ref.
NCT03552458	Effects of Probiotics in Preventing Oral Mucositis	HAN	*L. Reuteri*	O	
NCT03518268	Vivomixx for Prevention of Bone Loss in Women With Breast Cancer Treated With an Aromatase Inhibitor	BC	Vivomixx (*Lactobacillus* spp, *Bifidobacterium* spp)	O	
NCT03574051	Microbiota Associated With Iodine-131 Therapy and Hypothyroidism	TC	Probiotics (*B. infantis*, *L. acidophilus*, *E. faecalis*)	O	
NCT03642548	Probiotics Combined With Chemotherapy for Patients With Advanced NSCLC	NSCLC	Bifico (*B. Coagulans*)	O	
NCT02751736	The Effect Of Probiotics On Bowel Function Restoration After Ileostomy Closure In Patients With Rectal Cancer	CRC	*L. plantarum*	O	
NCT01790035	Probiotic LGG for Prevention of Side Effects in Patients Undergoing Chemoradiation for Gastrointestinal Cancer	GIC	*L. rhamnosus* GG	O	(101)
NCT00197873	*Lactobacillus rhamnosus* in Prevention of Chemotherapy-related Diarrhoea	CRC	*L. rhamnosus* GG	O	
NCT02544685	Prevention of Febrile Neutropenia by Synbiotics in Pediatric Cancer Patients	CAN	Probio-Fix Inum and corn starch (*L. rhamnosus* GG, *B. animalis*)	O	
NCT02819960	Prevention of Irinotecan Induced Diarrhea by Probiotics	CAN	Probio-Fix Inum (*L. rhamnosus* GG, *B. animalis*)	O	

CRC, colorectal cancer; CAN, cancer; PC, periampullary carcinoma; BC, breast cancer; LC, lung cancer; HC, hepatocellular carcinoma; PEDC, pediatric cancer; RCC, renal cell cancer; GIC, gastrointestinal cancer; GYC, gynecological cancer; HAN, head-and-neck cancer; TC, thyroid cancer; NSCLC, non-small cell lung cancer; LGG, *Lactobacillus rhamnosus* GG; C, closed study; O, ongoing study.

patients is supported by multiple *in vitro*, *in vivo* and clinical studies, as recently reviewed by our group (100). Moreover, 70 trials are currently registered at clinicaltial.gov, aiming to specifically determine the effects associated with the administration of LGG in several different conditions (Table II).

In line with these studies, a number of ongoing clinical trials are currently testing both the effectiveness and the safety of administering LGG to cancer patients subjected to anticancer therapy (NCT01790035, NCT00197873, NCT02544685, NCT02819960; Table I). Very recently, pre-results in support of the ongoing clinical trial NCT01790035 have been published. These results clearly show the mechanisms through which LGG is able to selectively protect colon normal cells during radiotherapy protocols, both *in vitro* and *in vivo*. LGG functions as a 'time-release capsule', able to deliver radioprotective lipoteichoic acid (LTA) within the intestinal crypts, thereby selectively protecting from the radiation-induced cell death the normal cells, but not the tumor cells (101). Notably, the group demonstrated that LGG-derived LTA activates peri-cryptal macrophages, in turn protecting the epithelial stem cells from radiation-induced apoptosis (101).

In addition to the cited clinical trials, two clinical trials designed by our group are currently opening and are about to be registered at clinicaltrials.gov. The two studies, entitled respectively: 'Maintenance of normal gastrointestinal function with dietary supplement containing *Lactobacillus rhamnosus* GG in cancer patients treated with cytotoxic chemotherapy and/or targeted therapy' and 'Maintenance of normal gastrointestinal function with dietary supplement containing *Lactobacillus rhamnosus* GG in patients treated with abdominal or pelvic radiotherapy', will assess the efficacy of LGG daily oral administration in the maintenance of normal gastrointestinal functions within cancer patients, treated either with chemotherapy and/or targeted therapy or abdominal/pelvic radiotherapy.

Once concluded, the currently ongoing clinical studies, will shed light into the efficacy and safety of the use of the promising probiotic, LGG, as an adjuvant in oncology. The studies will assess whether LGG is truly able to protect cancer patients from the detrimental gastrointestinal side-effects usually associated with anticancer therapy.

6. Conclusions

The human gut microbiota composition consists of a delicate balance, constantly modulated by several processes affecting the host during the entire lifespan (including aging, diet and lifetime exposure to heterogeneous environmental factors). A healthy microbiota is able to perform core symbiotic functions within his host, in a well-integrated host-microbiota relationship.

Cancer is a condition which tremendously affects the gut microbiota-host equilibrium, both during oncogenesis, as well as concurrently with anticancer therapy. This unbalanced

Table II. Clinical trials registered at clinicaltrials.gov assessing the benefits of administering LGG in association with a large number of different conditions.

NCT No.	Status	Conditions
NCT01922895	Active	Acute Alcoholic Hepatitis
NCT03080818	Active	Aging
NCT03449537	Active	Allergy Milk
NCT03256708	Active	Antibiotic-Associated Diarrhea
NCT03449459	Active	Chronic Obstructive Pulmonary Disease
NCT03587545	Active	Chronic Rhinosinusitis
NCT03647995	Active	Diarrhea, *Clostridium difficile*
NCT02544685	Active	Febrile Neutropenia
NCT01790035	Active	Gastrointestinal Neoplasms
NCT02640625	Active	Human Immunodeficiency Virus
NCT02748317	Active	Lower Urinary Tract Symptoms
NCT02748356	Active	Lower Urinary Tract Symptoms
NCT03383874	Active	Mania, Neurotic
NCT03215784	Active	Obesity, Pregnancy, Inflammation
NCT03277820	Active	Otitis Media
NCT03196453	Active	Overweight, Nutrition Disorder
NCT02462590	Active	Pneumonia, Infections, Diarrhea
NCT01454661	Active	Premature Infant
NCT00490425	Completed	Allergic Asthma
NCT01901380	Completed	Allergy, Functional Gastrointestinal Disorders
NCT00748748	Completed	Antibiotic-Associated Diarrhea
NCT02711800	Completed	Anxiety, Abdominal Pain
NCT00159523	Completed	Asthma, Atopic Dermatitis
NCT01148667	Completed	Atopic Dermatitis
NCT00325273	Completed	Atopic Dermatitis, Allergic Rhinitis, Asthma
NCT00224432	Completed	Atopic Dermatitis, Atopic Eczema
NCT03078179	Completed	Caries, Dental
NCT01279265	Completed	Colic, Inflammation
NCT02466035	Completed	Cow's Milk Allergy
NCT02779881	Completed	Cow's Milk Allergy
NCT01956916	Completed	Cystic Fibrosis
NCT01961661	Completed	Cystic Fibrosis
NCT00318695	Completed	Eczema, Asthma, Allergic Rhinitis
NCT02642289	Completed	Fibromyalgia
NCT01773967	Completed	Gastroenteritis
NCT02144701	Completed	Graft Versus Host Disease
NCT00620412	Completed	Healthy
NCT00934453	Completed	Healthy
NCT03168503	Completed	Healthy
NCT01274598	Completed	Healthy, Elderly
NCT01368029	Completed	Healthy, Elderly
NCT01545349	Completed	Healthy, Influenza
NCT03427515	Completed	Healthy, Stress-related Problem, Anxiety
NCT01969331	Completed	*Helicobacter pylori* Infection
NCT03307772	Completed	Herpes Labialis
NCT03310294	Completed	Herpes Labialis
NCT01439841	Completed	HIV-1 Infection
NCT01616693	Completed	Immunity to Oral Vaccines
NCT02046512	Completed	Infection
NCT01551186	Completed	Infectious Disease of Digestive Tract
NCT01130792	Completed	Infectious Gastroenteritis

Table II. Continued.

NCT No.	Status	Conditions
NCT02230345	Completed	Inflammation, Dyslipidemia
NCT01720329	Completed	Influenza
NCT03100266	Completed	Low Back Pain
NCT01164124	Completed	Low Birth Weight
NCT02288572	Completed	Metabolic Syndrome X
NCT01670916	Completed	Necrotizing Enterocolitis
NCT01868737	Completed	Necrotizing Enterocolitis
NCT02807246	Completed	Neonatal Hyperbilirubinemia
NCT02558192	Completed	Nosocomial Infection
NCT01870544	Completed	Obesity
NCT02444182	Completed	Periodontal Health, Dental Plaque Accumulation
NCT00282113	Completed	Premature Infants
NCT02180581	Completed	Respiratory Infections, Gastrointestinal Infections
NCT01229917	Completed	Respiratory Tract Infections
NCT02110732	Completed	Upper Respiratory Infection, Acute Otitis Media
NCT01782755	Completed	Ventilator Associated Pneumonia
NCT00445120	Completed	Vernal Keratoconjunctivitis

equilibrium is often followed by the dysbiosis of the gut microbiota. Consequently, current research is constantly aiming at identifying methods with which to safely modulate a dysbiotic microbiota, helping to heal detrimental conditions, such as the gastrointestinal side-effects of chemotherapy, radiation therapy and immunotherapy (including mucositis, diarrhea and opportunistic infections).

The administration of probiotics during anticancer therapy is yielding promising clinical results, as it improves gut dysbiosis in cancer patients. Moreover, probiotics have been found capable of significantly ameliorating patients' compliance to treatments, as well as their overall quality of life. Among the characterized probiotics, recent studies have suggested that LGG, administered *in vivo*, is able to modulate the immune system, reducing the detrimental toxic intestinal effects following pelvic radiotherapy. This result is particularly promising and paves the way towards the auspicious ongoing trials on cancer patients undergoing anticancer treatments.

Despite the already published clinical results reporting the beneficial role of probiotics in alleviating the harmful side-effects of anticancer therapies, care needs to be pursued, as patients are often immunocompromised; therefore, it is important to evaluate the health risks possibly linked to the administration of probiotics to sensitive individuals. In the future, the design of novel experimental trials may undertake a personalized approach, considering the specific clinical and pathological background of each single patient to be enrolled, in order to gain only the positive outcomes of probiotics administration, possibly without any harmful side-effect.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

ML is the PI of a research grant founded by Dicofarm Spa to his University Department. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interest.

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