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Revisión

Probiotic: effectiveness nutrition in cancer treatment and prevention

Probióticos: eficacia de la nutrición en el tratamiento y la prevención del cáncer

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Abstract

Among the neoplasias, colorectal cancer is one of the leading causes of cancer death in men and women. The increasing incidence of this type of cancer is due to the increase in the population's life expectancy, by the increase in chronic inflammatory bowel diseases, primarily ulcerative colitis and Crohn's disease, and the change in eating habits. The American Cancer Society (2011) shows that diet might be responsible for approximately 30% of cancer cases in developed countries, moreover when considering only colorectal cancer, the number can reach 30% to 50%. Probiotics are effective in the prevention and treatment of many bowel diseases as inflammatory bowel disease (IBD), diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis, *Helicobacter pylori* infection, and colon cancer. Classical examples are strains from the *Lactobacillus*, and *Bifidobacterium* genus that have probiotic proprieties with a potential use in the prophylaxis, as well as in the treatment of a variety of gastrointestinal tract disorders. Researchers are focusing on extremely important studies regarding the possibility of using probiotics to promote a balanced microbiota composition, and a sufficient immunological surveillance system as a way to prevent cancer. Considering the fact that the human intestines host 100 trillion bacteria, including more than 1,000 species, there is still need to perform more in depth investigations in order to find probiotics with potential to prevent, and treat cancerous diseases, adding a very promising effect to this already successful panorama. This revision aims to conduct a review of the most recent studies correlating probiotics and its cancer preventing and treatment potential.

Key words:

Colorectal cancer. Inflammatory bowel disease. Probiotics. Intestinal microbiota. Immune system.

Resumen

Entre las neoplasias, el cáncer colorrectal es una de las principales causas de muerte por cáncer en hombres y mujeres. El aumento de la incidencia de este tipo de cáncer es debido al aumento de la esperanza de vida de la población y al aumento de las enfermedades inflamatorias crónicas del intestino, colitis ulcerosa y principalmente la enfermedad de Crohn, así como el cambio en los hábitos alimenticios. La American Cancer Society (2011) muestra que la dieta podría ser responsable de aproximadamente el 30% de los casos de cáncer en los países desarrollados; por otra parte, cuando se considera solo el cáncer colorrectal, el número puede ser del 30% al 50%. Los probióticos son eficaces en la prevención y el tratamiento de muchas enfermedades intestinales como la enfermedad inflamatoria del intestino (IBD), la diarrea, el síndrome del intestino irritable, la intolerancia al gluten, la gastroenteritis, la infección por *Helicobacter pylori* y el cáncer de colon. Ejemplos clásicos son cepas de los géneros *Lactobacillus* y *Bifidobacterium* que tienen propiedades probióticas con un uso potencial en la profilaxis, así como en el tratamiento de una variedad de trastornos del tracto gastrointestinal. Los investigadores se están centrando en estudios muy importantes relacionados con la posibilidad de que el uso de probióticos pueda promover una composición de la microbiota equilibrada, y un sistema de vigilancia inmunológica suficiente como una forma de prevenir el cáncer. Teniendo en cuenta el hecho de que en los intestinos humanos viven 100 billones de bacterias, incluyendo más de 1.000 especies, todavía hay necesidad de realizar más investigaciones en profundidad con el fin de encontrar probióticos con potencial para prevenir y tratar enfermedades cancerosas, añadiendo un efecto muy prometedor a este ya exitoso panorama. Esta revisión tiene como objetivo realizar una revisión de los estudios más recientes que relacionan los probióticos y su potencial con la prevención y el tratamiento del cáncer.

Palabras clave:

Cáncer colorrectal. Enfermedad inflamatoria intestinal. Probióticos. Microbiota intestinal. Sistema inmune.

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INTRODUCTION

Responsible for an expressive and growing number of patients around the world, cancer is one of the main diseases responsible for morbidity and mortality of the world population (1). Cancer is classified as the second major death cause in different regions of the planet. In 2012 there was 14.1 million new cases and 8.2 million deaths; by 2030 it will be approximately 21 million cases and 13.2 million causalities, and, in Brazil, the estimative for 2014/2015 is around 576.000 new patients (2,3)

Among the neoplasias, colorectal cancer is one of the leading causes of cancer death in men and women (4,5). The increasing incidence of this type of cancer is due to the increase in the population's life expectancy, by the increase in chronic inflammatory bowel diseases, primarily ulcerative colitis and Crohn's disease, and the change in eating habits (6-8).

Colorectal cancer has a multifactorial etiology, associated to genetic mutations, diet, inflammatory processes, and, most recently, to the intestinal microbiota (9). According to Qin et al. (2010), human intestinal tract has a diverse and complex microbiota that interferes with the human health (10). Therefore, a disturb in its composition can lead to the development of several pathologies, for example, obesity (11,12), malnourishment (13), systemic diseases as diabetes (14), and chronic inflammatory disorders, like inflammatory bowel disease (15), that have an important effect on the pathogenesis of colorectal cancer (16).

The intestinal microbiota is characterized by its relentless dynamic (17).The diverse microbiota colonizing the gastrointestinal tract is not randomly formed. On the contrary, it is the product of a combination of factors, including environmental conditions, and variables such as age, diet, lifestyle, antibiotics therapy, genetic components, and exposure to pathogenic agents (18-23).

Some bioactive components, for instance probiotics, are important, and frequently used by the population. Recent studies have shown that probiotics can be beneficial to the human health, for example, decreasing the chance of developing cancer (24). There is evidence suggesting that some probiotics strains can affect the host's immunologic response, stimulating anti-inflammatory cytokines, antioxidants compounds, and generating anti-carcinogenic compounds (25). Thus, probiotics emerge as great alternatives for prevention, and treatment of a variety of gastroenterological conditions, for instance, inflammatory bowel disease, and colorectal cancer (26,27).

Taking into consideration the relevance of the subject, this work aimed to conduct a review of the most recent studies correlating probiotics and its cancer preventing and treatment potential.

CANCER

Cancer is a multifactorial disease that is originated by a progressive gathering of mutations in the cells genetic material (28). Between the alterations observed in the malignant tumors we can highlight: uncontrolled cell proliferation, growth factors insensibility, ability to invade surrounding tissues, and to migrate to distant sites originating new tumors (29-31).

As a general rule, cancer originates after a series of genetic alterations in the normal cell processess fundamental to the regulation of the cell cycle, cell signaling, and differentiation (32). According to Vermeulen et al. (2003), the cancer pathology is related to flaws in the mechanisms responsible for regulation of cell cycle, which allows mutated cells to go through the cycle, leading to the accumulation of genetic alterations, contributing to the development of malignant tumor characteristics (33).

According to Anand et al. (2008), only 5-10% of all cancer cases can be attributed to genetic defects, while 90-95% of the cases are related to external factors (34). According to the World Cancer Report (2014), around one third of all deaths caused by cancer are resulting from high body mass, low fruits and vegetables intake, sedentary life style, tobacco intake, and alcohol ingestion (3). The American Cancer Society (2011) shows that diet might be responsible for approximately 30% of cancer cases in developed countries and 20% in developing countries (35). Moreover, when considering only colorectal cancer, the number can reach 30 to 50% (36).

According to Wu et al. (2011), diet has major effects in human health, and, in part, due to their interaction with the intestinal microbiota (37). Studies show that diet affects the composition and metabolic activity of the intestinal flora, and that this, in return, can have an effect on the immune and inflammatory responses, having major consequences on the individuals's health (38). According to Anhe et al. (2013), an unbalanced diet can change the composition, and activity of the intestinal microbiota, consequently, leading to the development of several pathologies (39). On the other hand, consuming some types of food, for example, poultry, fish, fruits and vegetables, and, specially, bioactive components of functional foods can contribute to the prevention of many neoplasias, specially breast, prostate, and colon cancer (37,40-42).

INTESTINAL MICROBIOTA AND THE OCCURANCE OF INTESTINAL PATHOLOGIES

Around 100 trillion bacteria, with more than a thousand species, live in the human intestines, creating a symbiotic relationship with the host (43,44). The intestinal microbiota plays a crucial role in the development, and expansion of the lymphoid tissues, and in the maintenance and regulation of the immune system (17). Some microorganisms play a role in food digestion, and vitamin production, having an impact in the function and conservation of the gastrointestinal tract's health, as well as health in general, protecting the body against the attack of pathogenic microorganisms (45,46).

Although there are benefits from the intestinal microbiota on the host homeostasis, misbalance in its composition, resulting in alteration of its function, can lead to the development of several pathologies (47,48). According to Cho et al. (2012), the appearance of an increasing number of diseases, such as inflammatory bowel disease, type 2 diabetes, obesity, allergies, and colorectal cancer are directly related to alterations in the function and composition

of the intestinal microbiota (49). Inflammatory bowel disease (IBD), like Crohn's disease (CD), and ulcerative colitis (UC), are chronic inflammatory diseases, with an unknown etiology, that affect the gastrointestinal tract, being them both related to the development of colorectal cancer (8,50-52). Patients with CD show a cumulative elevated risk of developing colorectal cancer, from 2.9% in 10 years, to 8.3% after 30 years of the disease onset (53).

A recent meta-analysis was performed aiming to evaluate the risk of developing colorectal cancer associated with CD. It was shown that, in 34 studies, approximately 60,000 patients diagnosed with CD also showed subsequent cancers (54). On the same way, Basseri et al. (2012) identify that 5.6 % of the individuals diagnosed with CD developed cancer or dysplasia due to the disease complications (55).

Colorectal cancer was the most common cause of death in the USA by the end of the 1940s and beginning of the 1950s (56). According to the latest world estimative, colorectal cancer is the third most common cancer type, and the third main cancer death cause in men and women (3). Data from the World Health organization show that together with lung, liver, and breast cancers, colorectal cancer is responsible for the majority of cancer deaths each year (57).

In Brazil, colorectal cancer is responsible for more than 15,000 deaths in 2013 (58). Considering the period between 2014-2015, the occurrence of approximately 33,000 new colon and rectal cancers were documented, with an estimated risk of 15.44 new cases/100,000 men, and 17.24 cases/100,000 women (3).

Intestinal bacteria can have a positive effect on the immune system defense against cancer by modulating the host immune function. Researchers have been focusing on extremely important studies regarding the hypothesis that probiotics can promote an equilibrated bacterial population, and an immunological vigilance system that would be satisfactory to prevent cancer. Functional food can be used as a strategy to prevent the development of cancer and protect against its causes, as previously mentioned.

IMMUNE SYSTEM AND INTESTINAL MUCOSA

The immune system is complex, involves multiple interactions between organs, cells, and molecules, with the main purpose of defending the body against antigens. Numerous antigens penetrate the body through the mucosa, so, the host mucosa immune system play a key role in the immune defense against pathogens (59,60). Moreover, around 80% of the immune cells are associated with the intestinal mucosa (61).

The immune response can be innate or adaptive. The innate immune response is fast, unspecific, and includes mostly phagocytes, such as neutrophils, monocytes, macrophages, denditric cells, and natural killers (NK). The adaptive response, on the other hand, is slower, and characterized by its specificity and memory, being B and T lymphocytes the main cells involved in the response. T lymphocytes can be categorized as helper T cells (CD4 +, also known as T helper – Th) and cytotoxic T cells (CD8 +). T helpers are found mainly in two distinct cells, Th1 and Th2, that are set apart by their cytokines and immune response. Th1 cells synthesize pro-inflammatory cytokines able to stimulate the inflammatory response, while Th2 cells produce anti-inflammatory cytokines that can attenuate inflammation (60,62).

The balance between Th1 and Th2 activity in cytokine production can determine the direction and result of the immune response. An exacerbated response towards Th1 is associated to chronic inflammatory diseases, while an abnormal Th2 response characterizes allergic, and autoimmune reactions (60).

Cytokines

Cytokines are extracellular, water soluble polypeptides or glicoproteins secreted by a variety of cells. A single cell can secrete the same cytokine, which has a paracrine or autocrine signaling. Similar activities can be unveiled by different cytokines, and its secretion occurs, usually, in cascade (63).

Several interactions between immune system cells are controlled by cytokines. They can influence the activity, differentiation, proliferation and survival of the immune cells, in addition to regulating the release, and activity of other cytokines (64).

Cytokines are central mediators that guide the inflammatory response to the lesion, and infection sites. Conversely, an exacerbated release of pro-inflammatory cytokines from the lesion site can lead to serious damage to the body, but anti-inflammatory cytokines can minimize some of these undesired effects (65).

Macrophages, monocytes, eosinophils, hepatocytes, and glial cells secrete Interleukin 6 (IL-6), and the tumor necrosis factor (TNF-α), and IL-1 are potent inducers. IL-6 is an important pro-inflammatory cytokine that promotes maturation and activation of neutrophils, maturation of macrophages, and differentiation and/or maintenance of cytotoxic T lymphocytes, and NK cells. TNF-α is another important pro-inflammatory cytokine, produced mainly by monocytes, macrophages and T lymphocytes. After a surgical procedure, trauma or during an infection, TNF-α is one of the first, and most potent mediators of the inflammatory response, with the capability to make changes in the metabolism, and activate other cytokines (63,64). IL-10, on the other hand, is an example of anti-inflammatory cytokine, synthesized by immune cells, and neuroendocrine, and neural tissues. IL-10 has the ability to inhibit pro-inflammatory cytokines and stimulate the endogenous production of anti-inflammatory cytokines (66).

The current knowledge on how probiotics affect the immune system was obtained mainly by analyzing the cytokine profile produced by several immune cells in response to the consumption of probiotic microorganisms. For every new probiotics isolate, the secreted cytokine profile needs to be established, once the beneficial health effect is different for each isolate (59).

In vitro studies are used to establish the cytokine profiles. To perform those tests, the physiological conditions need to be replicated. Lipopolysaccharide (LPS) is a gram-negative bacterial cell wall component that acts on mammal cells, mostly macrophages, inducing the release of cytokines (67). LPS is a common tool to simulate inflammation *in vitro* in order to quantify cytokines release (68,69).

The maintenance of the balance between the pro-inflammatory and anti-inflammatory activity is essential to the human health. Therefore, studying the cytokine modulation caused by a microorganism is an important step in the probiotic selection (69).

Ashraf and collaborators (2013) after stimulating peripheral mononuclear blood cells with microorganisms from the *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, and *Streptococcus* genus showed an increase in cytokines expression, including TNF-α, and IL-10 (68). Morita and colleagues (2002) also showed a significant increase in IL-6, IL-10, IL-12, and TNF-α cytokines after stimulation of rat macrophages with BAL *Lactobacillus acidophilus* TMC 0356 (70).

PROBIOTICS

Probiotics, "live organisms that, when administered in adequate amounts, have beneficial effects on the host's health", can survive in the intestines and promote the recovery of normal intestinal microbiota, being *lactobacillus* and bifidobacteria the most well known (71).

PROBIOTICS AND IMMUNE SYSTEM

Probiotics help on the regulation of the immune response and its continuous use is advantageous to its consumer's health, participating in the modulation of normal intestinal microbiota, reducing the risk of intestinal disorders, preventing diseases like infections, and food allergies, reducing cholesterol levels, stabilizing the intestinal mucosa, and relieving the lactose intolerance symptoms (72-77).

Considering that approximately 80% of the immune cells are related to the intestinal mucosa, probiotics that have the ability to adhere to the intestinal epithelium, and interact with immune cells, play a crucial role in the modulation of the immunological response (61,69).

The effect of the bacterial compounds released in the lumen and absorbed by the intestinal epithelium, as well as the alterations of the cell physiology due to the bacterial contact have been considered as the plausible mechanism by which probiotic microorganisms affect the immunological function, either local or systemically (78). Then again, is important to highlight that the probiotic's immuno modulatory effect is different for every isolate, diverging on the cytokine expression profile, and in the regulatory T cell response (59,68).

Probiotics affect the immune system through the innate and adaptive immune system cells. Stimulation of phagocytes, and the increase of NK cytotoxicity, enhances the inhibitory effect over tumors, and infections (79). The efficiency of the NK cells can also be increased when a combination of probiotics and dextran is used (80). These studies suggest that probiotics can play an important role in reinforcing the immunological surveillance of the NK cells, helping to avoid the development of malignant tumors (59). Moreover, probiotics seem to increase the release of immunoglobulin IgA and IgM, reinforcing the adaptive immune response (61).

Those studies suggest that probiotics consumption can affect the differentiation of T helper lymphocytes, altering the balance between the production of Th1 and Th2 lymphocytes (59,81-83). Considering that probiotics have the ability to reinforce the innate, and adaptive immune response its potential as nutritional supplements have been exploited in order to improve the immune system response in age specific groups, such as elderly (78,79).

INTESTINAL EPITHELIUM ADHESION ABILITY

The microorganism's ability to adhere to the intestinal epithelium is an important feature, allowing probiotics to have its beneficial effects to the health, including the inhibition of the pathogenic microorganisms, and the modulation of the immune system. Thus, adhesion is one of the main selection criteria for probiotic microorganisms. Moreover, the adhesion capability of bacteria plays an important role in the intestine colonization, avoiding the elimination by the peristaltic movements (61,84-86).

The interaction between the probiotic microorganisms and the enterocytes is fundamental to the early stages of the immune system modulation, and for an adequate cytokine production. Therefore, models that reproduce the mucosa on a cellular level should be the desired ones when evaluating the immune function of probiotics, once stimulation of the immune response in blood cells is not physiologically accurate (59).

Motivated by the desire to elucidate cancer mechanisms, researches like Fogh and collaborators started studies in the 1970s, and established lineages collections from intestinal tumors. Caco-2 (87), and HT-29 (88), both human epithelial colorectal adenocarcinomas, were some of the lineages established.

Caco-2 and HT-29 were effectively used to verify the adhesive properties in several studies (61,70,77,84,85,89). *In vitro* studies can be used as tools to predict the survival of *Lactobacillus* spp lineages in the gastrointestinal tract, and to evaluate the adhesion ability to Caco-2 cells (90).

PROBIOTIC ANTI-INFLAMMATORY ACTIVITY

Several evidences have proven that it is the probiotics activity leading to the production of pro- and anti-inflammatory cytokines that promotes the development and maintenance of an alert state of the innate, and adaptive immune systems, and reduce the ability of the host's immune response to unbalanced inflammatory conditions (91). Probiotics contribute to the inhibition of the exacerbated immune responses, which might have beneficial effects against the development of chronic intestinal diseases, and autoimmune diseases (59). Additionally, studies suggest that probiotics could help controlling malignant tumors development thought the reinforcement of the immunological surveillance triggered by NK cells (59).

IBDs are chronic gastrointestinal tract inflammation, characterized by a misregulation of the immune system, leading to a

chronic inflammatory response (63). In Crohn's disease, the predominant inflammatory response is mediated by Th1 lymphocytes. Contrarily, ulcerative colitis immune response is mediated by Th2 lymphocytes (92,93).

Cytokine profiles play an important role in the maintenance of the intestines immune system homeostasis. Probiotics can attenuate the bowel inflammation in IBD by decreasing the inflammatory mediators production, and modulating the anti-inflammatory cytokines expression (94). By the increase in IL-10, and decrease in inflammatory cytokines like TNF-α, some probiotics can prevent the onset of local inflammatory diseases, being potentially used as an adjunct therapy to conventional treatments (66).

Wang and collaborators evaluated the anti-inflammatory effect of *Bifidobacterium animalis subsp. lactis*, and showed that a proteic, soluble factor secreted by the bacteria has the ability to inhibit pro-inflammatory cytokine TNF-α. Results from this study indicate that there is a potential application of probiotics in the prevention of bowel disease lesions mediated by inflammatory cytokines (95).

As a general rule, the synthesis of microbial substances that act on pathogenic bacteria, change in the intestinal pH, competition for essential nutrients that enable pathogenic microorganisms growth, increase in mucosa secretion, toxins and its receptors inactivation, and stimulation of phagocytosis, as well as specific and nonspecific immune responses against the pathogenic agents seems to be the most likely mechanisms by which probiotics promote the body homeostasis (96,97).

The immunomodulatory effect of probiotics varies according to the strain, diverging in the cytokine expression profile, and the regulatory T cell response. Thus, it is important to determine the effect for every new strain, allowing the validation of its pro-, and anti-inflammatory properties, as well as the possible clinical application (59,68). Likewise, clinical studies in humans are necessary to prove the efficacy of probiotics in the treatment of inflammatory bowel disease, and other inflammatory diseases, as well as determine the therapeutic applications, and the mechanisms involved in these beneficial processes (66).

PROBIOTICS THERAPEUTIC APPLICATIONS

Recently, there is a growing interest in functional food and how they promote and maintain a good health. The consumption of food supplements has grown in the international market reaching millions of consumers. Among the food with probiotic properties the most popular ones are fermented milk products like yogurt, cheese, kefir, and ice cream (77,98-101). The fermented product commercially known as 'Yakult', a Japanese brand, containing *Lactobacillus casei* Shirota *in vivo* is the bestseller product in the world (102).

Probiotics are effective in the prevention and treatment of many bowel diseases as inflammatory bowel disease (IBD), diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis, *Helicobacter pylori* infection, and colon cancer (103,104). Clinical studies in humans use several probiotics treatments, and a placebo control. Results generate important evidence regarding probiotic use, with significative effectiveness in the treatment of several gastrointestinal diseases (105,106).

Furthermore, the clinical studies also identified two mechanisms of action by which probiotics mediate the maintenance of the gastrointestinal microbiota balance: a) production of antibacterial substances, and the competitive inhibition of the pathogen; and b) toxins adhesion to the intestinal epithelium. Gram-positive bacteria *Lactococcus lactis* synthesizes antimicrobial peptides, and is an example of the first mechanism of action. Acetic, lactic, and propionic acid produced by *Lactobacilli* strains reduce the pH, inhibiting the growth of several pathogenic gram-negative bacteria. As an example, some *Lactobacillus* strains produce lactic acid inhibiting *Salmonella enterica* growth (107).

Lactobacilli and Bifidobacteria have the capability of competing with pathogenic bacteria such as *Bacteroides vulgatus, Clostridium histolyticum, C. difficile, Enterobacter aerogenes, Listeria monocytogenes, Staphylococcus aureus, Salmonella enterica, Yersinia enterocolitica*, and *Escherichia coli*, dislocating it from the intestinal epithelium, as an example for the second mentioned mechanism of action. Studies regarding these probiotics refer to them as blockers of pathogenic agents once they alter the membrane carbohydrate receptors in the intestinal epithelium (108,109). Blocking of the bacterial enterotoxin binding seems to be a promising therapeutic tool.

Bifidobacteria have beneficial effects in the prevention, and relieve of infectious diarrhea, and an improvement in the symptomatology of inflammatory bowel disease (110). Specific lineages of bifidobacteria suppress genes that are induced by *H. pylori* in human epithelial cells (111), while *Bifidobacterium* sp. has inhibitory activity against *Streptococcus mutans*, and *Streptococcus sobrinus*, etiological agents strongly associated with dental cavities in humans (112). Lim et al. (2015) showed that some yeast increase the growth of other probiotics under acidic conditions, like *Saccharomyces cerevisiae* CE-1118, that improves the viability of the probiotic *Lactobacillus rhamnosus* HN001 under pH 2.5-4 (113).

Recent studies, as the one performed by Jungersen and collaborators (2014), proved the efficacy of *Bifidobacterium animalis* subsp. *lactis* BB-12® in the improvement of the bowel function, protection against diarrhea, and reduction of antimicrobial therapy adverse effects. In addition, the authors showed that individuals had an increased resistance to common respiratory infections, and a decreased incidence of acute respiratory infections (61).

These clinical studies showed that a combination of six probiotic bacteria (*L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum*, and *B. infantis*) inhibit the growth of pathogenic bacteria in patients with severe acute pancreatitis (114).

Many studies showed that probiotics assist in the prevention and treatment of *Clostridium difficile* associated diarrhea (CDAD). Gao et al. (2010) identified a decreased incidence risk after a prevention treatment with two strains of *Lactobacillus* (115). *Saccharomyces boulardii* has also been successfully used for the treatment of CDAD (116).

Saccharomyces boulardii is a well-studied probiotic that acts in several gastrointestinal disorders. In its lyophilized form, it is effective for the diarrhea treatment by reducing the length of the disease independently of the cause (117-119).

Recently, *Akkermansia muciniphila* was described as a potential probiotic, residing in the intestinal mucus layers (120). Many studies have shown that this bacteria level is reduced in the gastrointestinal tract of obese patients (121,122). This bacteria is known to metabolize a variety of complex carbon hydrates, as well as synthesize many amino acids and vitamins (123). Shin et al. (2014), performing *in vivo* assays in rats, identified that the bacteria induced the expression of regulatory T cell Foxp3 in the visceral adipose tissue, which attenuates inflammation (124). Considering these results, it was suggested that *A. muciniphila* could be useful in the diabetes treatment.

Faecalibacterium prausnitzii, another organism strongly related with the human gastrointestinal microbiota, has also being well investigated. It represents around 5-15% of the total fecal microbiota, being one of the major butyrate producers in the gastrointestinal tract (125,126). Butyrate is essential to maintain the integrity of the epithelial barrier, which is consider a primarily energy source in the intestines. This compound has a valuable importance in reducing cancer progression, protecting against pathogens, and stimulating the immune system (127).

In this way, probiotics help to promote homeostasis by several mechanisms in the intestinal epithelial cells (91).

CONCLUSIONS

Cancer is a disease responsible for an expressive, and growing number of cases in the world, being colorectal cancer one of the main death causes by cancer in men and women in the world (4,5). One of the reasons for the increased incidence of this kind of cancer is the prevalence of chronic gastrointestinal epithelium inflammatory disorders, mainly represented by ulcerative colitis, and Crohn's disease (6-8).

The need to find alternatives that can assist in the treatment and prevention of inflammatory bowel disease, and colorectal cancer, make probiotics a promising source. They play a crucial role in the modulation of the immune response, considering that approximately 80% of the immune cells are associated to the intestinal membrane (61,69).

Probiotics have a vast, and successful applicability. Classical examples are strains from the *Lactobacillus*, and *Bifidobacterium* genus that have probiotic proprieties with a potential use in the prophylaxis, as well as in the treatment of a variety of gastroinstetinal tract disorders. Recently, another example is the new probiotic species *A. muciniphila* that is being tested in animal assays, and in clinical trials with promising results regarding its favorable activity on the treatment or diagnosis of gastrointestinal tract diseases.

Researchers are focusing on extremely important studies regarding the possibility of using probiotics to promote a balanced microbiota composition, and a sufficient immunological surveillance system as a way to prevent cancer. Considering the fact that the human intestines hosts 100 trillion bacteria, including more than 1,000 species, there is still need to perform more in depth investigations in order to find probiotics with potential to prevent, and treat cancerous diseases, adding a very promising effect to this already successful panorama.

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