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Lactobacillus acidophilus associated with other probiotics alters the microbiota of colorectal cancer patients: systematic review

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Abstract

Objective: Microbiome is an important factor for the development and progression of colorectal cancer. The aim of the study was to carry out a systematic review to verify whether the administration of food or pharmaceutical formulations containing the bacterium *Lactobacillus acidophilus*, alone or associated with other bacteria and substances could alter the intestinal microbiota in colorectal cancer patients. **Methods:** The review of randomized trials compared the use of *L. acidophilus* versus placebo or samples of healthy patients without intervention. **Results:** Two independent reviewers performed the search and found 1,060 articles, with the preliminary selection of 22 articles that were read in full and 04 articles that were included in the systematic review. The included articles worked with pharmaceutical formulations containing *L. acidophilus* associated with other probiotic bacteria and prebiotic fibers. The results showed that the administration of formulations in patients with colorectal cancer was for less than 31 days, underwent colonoscopy or surgical resection with qualitative and quantitative changes in the microbiota of the individuals included compared to those who received placebo formulation or were under healthy control. **Conclusions:** The alterations found demonstrate that probiotics had the ability to modulate the microbiota to a profile close to that found by healthy patients.
Keywords: probiotics, colorectal neoplasms, dietary supplements, evidence-based medicine.

Lactobacillus acidophilus associado a outros probióticos altera a microbiota de pacientes com câncer colorretal: revisão sistemática

Resumo

Objetivos: Microbioma é um fator importante para o desenvolvimento e progressão de câncer colorretal. O objetivo do trabalho foi realizar uma revisão sistemática para verificar se a administração de formulações alimentícias ou farmacêuticas contendo a bactéria *Lactobacillus acidophilus*, de forma isolada ou associada a outras bactérias e substâncias poderia alterar a microbiota intestinal em pacientes com câncer colorretal. **Métodos:** A revisão de ensaios randomizados comparou o uso de *L. acidophilus* versus placebo ou amostras de pacientes saudáveis sem intervenção. **Resultados:** Dois revisores independentes realizaram a busca e encontraram 1060 artigos, com a seleção preliminar de 22 artigos que foram lidos na íntegra e 04 artigos que foram incluídos na revisão sistemática. Os artigos incluídos trabalharam com formulações farmacêuticas contendo *L. acidophilus* associado com outras bactérias probióticas e fibras prebióticas. Os resultados demonstraram que a administração das formulações em pacientes com câncer colorretal foi por período inferior a 31 dias, passaram por colonoscopia ou ressecção cirúrgica tiveram alterações qualitativas e quantitativas da microbiota dos indivíduos incluídos em comparação com os indivíduos que receberam formulação placebo ou eram do controle saudável. **Conclusões:** As alterações encontradas demonstram que os probióticos tiveram a capacidade de modular a microbiota para um perfil próximo ao encontrado por pacientes saudáveis.
Palavras-chave: probióticos, neoplasias colorretais, suplementos nutricionais, medicina baseada em evidências.

Introduction

Colon and rectal cancer, also called colorectal cancer (CRC), is the third most prevalent malignant neoplasm in the world, according to mortality, representing 10% of all cases of neoplasms. It is the second malignant neoplasm most usually diagnosed in women and the third most frequently diagnosed in men, with 1.9 million cases and 95,000 deaths in the world. In Brazil, it is the second most common type of cancer diagnosed in both genders, with an increasing rise in the mortality rate. In addition to the impact on mortality, it is a disease that affects the patients' quality of life and their work and family routine, affecting their personal and collective expenses, through hospital care for hospitalizations and treatments.[1,2]

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The CRC forms involve malignant tumors located in the large intestine, in the rectal and anal regions, being treatable and curable when it does not present metastases to other organs. When diagnosed in early stages, CRC can be treated with surgical resection, chemotherapy and radiotherapy, treatments that drastically reduce the patient's quality of life. Consequently, the prevention strategy is interesting to deal with this type of cancer.[3,4]

For such purpose, it is important to know the factors related to development of the pathology, thus allowing use and development of prophylactic methods. Various factors are involved in CRC development, from genetic to environmental. However, diet is the main risk factor, estimating that 90% of the cases could be prevented by implementing interventions in the eating habits. Diet can even modulate the intestinal microbiota, either promoting its protection or increasing the risk of carcinogenesis.[5,6]

Composition of the microbiome is another factor related to CRC development and progression, enhancing its development, through pathogenic bacteria and their metabolites that act in a DNA mutagenic way; or preventing, through probiotic bacteria which secrete substances that inhibit adhesion of pathogenic bacteria and reinforcing the barrier protection of intestinal cells, preventing translocation of pathogenic microorganisms into these cells or into the blood stream.[7,8,]

In this sense, the concept of probiotics emerges, which are microorganisms that, when administered in adequate amounts, confer benefits to the host organism, such as intestinal balance through microbiome modulation, stimulation of the immune system and prevention of the carcinogenic activity of bile salts. In order to have high resoluteness in their activity, probiotics need suitable substrates that can be metabolized into short-chain fatty acids (SCFAs) such as butyrate and propionate, which act by providing energy to the colonocytes, while reducing the pH of the large intestine, a mechanism that reduces adhesion of the pathogenic bacteria involved in CRC development.[4]

The increasing use of probiotic bacteria in food products and pharmaceutical formulations claims, among other benefits, that the use of these microorganisms could assist in microbiota modulation, for a microenvironment less favorable to the development of pathogenic bacteria. In this context, the *Lactobacillus acidophilus* lactic acid bacterium stands out, which is a probiotic bacterium with recognized action in reducing abdominal pain or discomfort in patients with irritable bowel syndrome, as well as in the reduction of total cholesterol, LDL cholesterol, triacylglycerols and reduction of insulin resistance.[9]

In the case of colorectal cancer, *in vitro* and *in vivo* tests in rodents have shown that *L. acidophilus*, either alone or in combination with probiotic bacteria, or even associated with prebiotics (soluble fibers that can be fermented by probiotics), reduces the quantification of cancer-related markers (such as DNA damage, aberrant crypt foci in the colon and quantitative and qualitative reduction of tumors).[10]

However, there is no definitive evidence that probiotics reduce the risk of colorectal cancer in humans, as the data are inconsistent, and there are epidemiological studies showing that high consumption of fermented dairy products containing *Lactobacillus* or *Bifidobacterium* is related to low risk of developing cancer, while some population genetics studies have related high risk of developing cancer with intestinal microbiota with a high amount of certain *Bifidobacterium* species.[10]

Considering that an intestinal microbiota composed of bacteria with probiotic characteristics in wide and varied amount and diversity is related to a preventive potential and that a diverse microbiota has an inducing effect on CRC development, the objective of the study was to conduct a systematic review to verify the effectiveness of administering *L. acidophilus* alone or in combination with other probiotics and prebiotics in modulating the microbiota in a beneficial way.

Methods

The systematic review was conducted by two independent researchers from January 2017 to February 2018, in accordance with the criteria recommended by the "Cochrane Handbook for Systematic Reviews of Interventions" and using the checklist proposed by the PRISMA methodology.[11]

Thus, the design was carried out according to the PICOS strategy, in which the population considered (P) was patients with colorectal cancer monitored by a group of studies authorized by the Committee of Ethics in Human Research in the administration of medications and/or food products, the intervention (I) was the administration of these food products or medications containing *Lactobacillus acidophilus* alone or in combination with other probiotic strains and other food substances (fibers, for example), the control was the placebo (C) and/or non-use of probiotics, and the outcome (O) was defined as alteration of the non-pathogenic and pathogenic microbiota. Finally, the studies included in this review were those conducted *in vivo* based on biological material from patients with CRC who consumed probiotics.

To conduct the research, the systematic search for the articles was performed in the following databases: Medline, Science Direct, Cochrane Central Register of Controlled Trials, Scopus, Web of Science and SciELO. The articles selected were those written in Portuguese, Spanish and English, with no restrictions regarding year of publication. The search strategies consisted of the terms "colorectal cancer", "*Lactobacillus acidophilus*", "probiotics" and "randomized controlled trial", associated with the Boolean operators AND or OR, being adjusted according to the database.

The clinical studies retrieved had their titles and abstracts evaluated regarding eligibility criteria, namely:

- Studies carried out with food products containing probiotic bacterium *Lactobacillus acidophilus* exclusively or not, with the possibility that the product is associated with other bacteria.
- Studies conducted with medications that contained *Lactobacillus acidophilus* and which, regardless of the pharmaceutical presentation (solution, capsule, sachet, etc.), were absorbed by the intestinal mucosa.

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Studies associated with yeasts, cohort studies, bibliographic reviews, systematic reviews, meta-analyses, book chapters, dissertations, theses, abstracts and expanded abstracts were not included in the research. Clinical studies containing probiotic bacteria but not including *Lactobacillus acidophilus* in the association were also not included. Studies that, in addition to patients with CRC, had other pathologies related to the non-neoplastic gastrointestinal tract were also excluded

Subsequently, the articles selected in the initial screening were evaluated in their full content, and thus, being excluded or maintained permanently in the review, according to the judgment of the main evaluator.

Data extraction from the studies selected was performed using Microsoft Office Excel 2013® and the Endnote Web® X8 program was used for data management.

The data extracted show general characteristics of the study, such as the matrix in which the probiotic was (pharmaceutical presentation or food), if it was exclusive or in association with other bacteria, the concentration used, study population, study time and the methodology(ies) for obtaining the result(s) among other items. When necessary, the authors of the studies were contacted, either for general clarifications or for sharing results not presented in the articles.

The quality assessment was carried out according to the Cochrane Collaboration tool to assess risk of bias in randomized clinical trials, using the parameters defined in Annex II, through the Review Manager 5.3 software (Cochrane Collaboration, 2014, Cochrane Nordic Center, Copenhagen, Denmark).

Results

A total of 1,060 potential studies were found during the research study in the following databases: Medline (n = 67), Embase (n = 0), Science Direct (n = 693), Cochrane (n = 11), Scopus (n = 131), Web of Science (n = 155) and SciELO (n = 3). Of these, 798 articles were excluded by the EndNote tool due to duplication. Consequently, 262 articles had their titles and abstracts evaluated according to the inclusion and exclusion criteria established for the research. In this stage, 240 articles were excluded and 22 were selected, which were read in full resulting in the inclusion of 04 articles in the systematic review (Figure 1).

A total of 04 articles were included, encompassing the time interval from 2011 to 2017 and conducted in Sweden (01 article) and in China (03 articles).

Of the articles excluded after reading them in full, 01 was excluded for presenting different outcomes (quality of life) than those proposed by the current study and 17 were excluded for not complying with the study design (studies with exclusive use of *Bifidobacterium*, with probiotic associations and without *L. acidophilus*, studies with yeasts, non-randomized studies and studies where the individuals did not have CRC or there was an association with other groups of patients).

In general terms, the methodological quality of the articles selected was considered adequate, taking into account that the risk of bias was low (Figure 2). This was due to the fact that three of the four studies were properly randomized using a computer.[12, 13, 14] One article[15] had its randomization considered as with unclear risk of bias, as the authors did not explain how it was performed in relation to the patients.

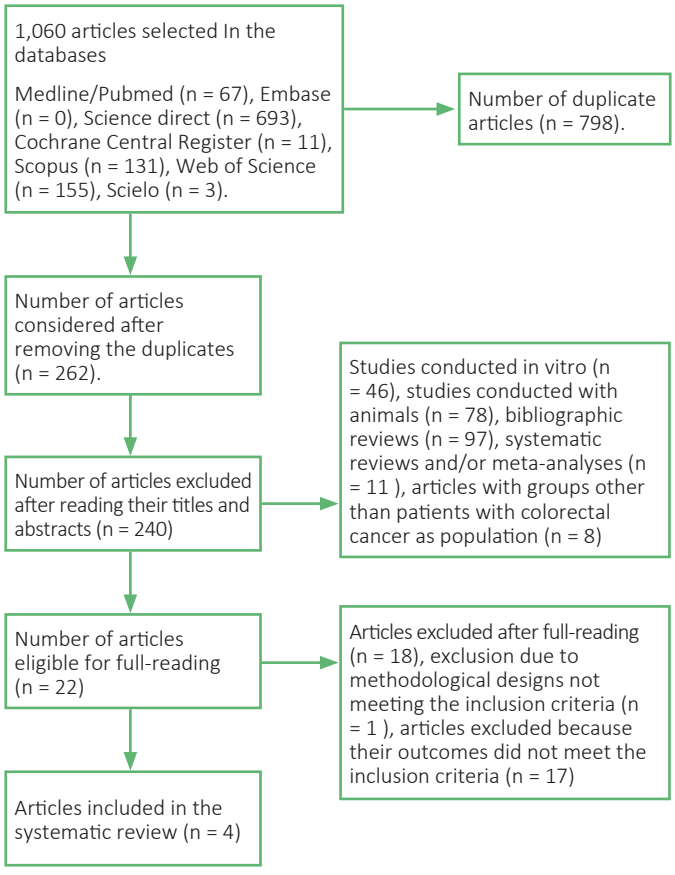
Two articles[13,14] divided the subjects into two groups (probiotics and placebo). Administration was through capsules and powders. Two studies[12, 15] divided the subjects into two groups (probiotic and placebo and/or non-probiotic control) and added a third group of healthy subjects for sample comparison.

Treatment allocation was considered adequate for three, as preparations containing probiotics and placebo preparations had similar packaging, appearance, aroma and flavor in four studies.[12, 13, 14] One article did not describe how allocation of the treatments was made or if there was placebo, thus being considered as with unclear risk of bias.[15]

Despite the unclear risk of bias, the study by Hibberd et al[15] was included in the research, as it evaluated alteration of the microbiota through the molecular biology methodology, with no other results that showed any bias for a specific clinical parameter (such as decreased constipation or decreased diarrhea), considering the article suitable for evaluation.

It was determined that there was high risk of bias in the "Other types of bias" item in the paper by Hibberd et al,[15] due to the fact that one of the authors worked at the company that manufactured the capsule containing probiotics that was analyzed (ProBion Clinica, WasaMedicals AB, Halmstad, Sweden).

Figure 1. Flowchart corresponding to the selection of the studies included in the research.



Source: Adapted from PRISMA

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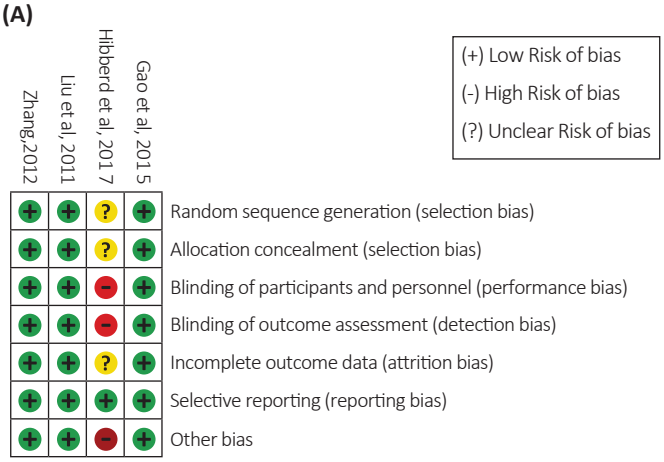
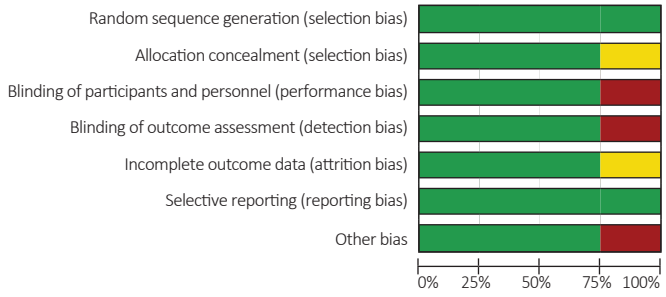
Figure 2. (A) Summary of the risk of bias: determination of the authors of the review regarding each risk of bias for each of the articles included. **(B)** Risk of bias graph: determination of the authors of the review regarding each risk of bias, presenting the percentages of all the studies included.

(A)



(B)



Source: Adapted from PRISMA

Of the 04 studies included, 03 were double-blind, that is, neither the patients nor the researchers knew who was receiving the placebo and who was receiving the study intervention, and this function was performed by a third person who was only in charge of the administration (generally, some nurse from the place where the study was carried out or the pharmacist responsible for handling the samples) (Table 1).

The study conducted by Hibberd et al[15] did not explain whether blinding was performed for the patients or how the action was performed for the patients with CRC who did not use probiotics, whether they received placebo or not.

All studies used an elective surgical procedure, with patients who had a minimum waiting time and without immunosuppression, thus allowing for preoperative intervention with probiotics and, in some studies, also after it. As an in-hospital routine practice, antibiotic therapy was also performed

With a total of 229 participants in the four studies, 99 patients were in the experimental group using probiotics, 98 were in the placebo experimental group, and 33 healthy subjects were included to provide healthy tissue samples for the research (Table 2).

All the studies included used *Lactobacillus acidophilus* associated with other probiotic bacteria. *Bifidobacterium longum* was the main probiotic bacterial species used in association with *L. acidophilus*, and was found in three papers. *Enterococcus faecalis* was the second most used species in association, and was found in two papers. Only one paper associated prebiotics with probiotics, in the case of insulin in association with *L. acidophilus*[15] (Table 3).

Tabela 1. Características dos estudos incluídos na revisão sistemática

Author	Country	Type of study	Study design	
			T	C
Hibberd *et al*, 2017	Sweden	Randomized, not blinded, with control without placebo, with CRC and control with health individuals.	ICP + ATB + PRO + Colectomy	Colectomy and Colonoscopy for healthy individuals
Gao *et al*, 2015	China	Randomized, double-blind, control with placebo and control with healthy individuals.	ICP + ATB + PRO + Colectomy	ICP + ATB + Placebo + Colectomy and colonoscopy for healthy individuals
Zhang *et al*, 2012	China	Randomized, double-blind and control with placebo.	ICP + ATB + PRO + Colectomy	ICP + ATB + Placebo + Colectomy
Liu *et al*, 2011	China	Randomized, double-blind and control with placebo.	ICP + ATB + PRO + Colectomy	ICP + ATB + Placebo + Colectomy

Key: CRC: Colorectal Cancer: PRO: Probiotics; T: Treatment; C: Control ICP: Intestinal Cleansing Procedure; ATB: Antibiotic Therapy

Table 2. Characteristics of the patients and of the treatments used in the studies selected

Author	Age (Mean ± SD)	
	T	C
Hibberd *et al*, 2017[14]	63 (55 – 73)	77 (68 – 75)
Gao *et al*, 2015[11]	65 ± 5.96	71 ± 5.4/68 ± 7.3**
Zhang *et al*, 2012[12]	67.5 (45 – 87)	61.5 (46 – 82)
Liu *et al*, 2011[13]	65.3 ± 11.0	65.7 ± 9.9

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Table 3. Characteristics of the treatments used in the studies selected

Author	Intervention		Length of the intervention (days)
	T	C	
Hibberd *et al*, 2017[14]	Tablets with 1.4×10^{10} UFC *Bifidobacterium lactis* Bl-04 and 7×10^{9} UFC *Lactobacillus acidophilus* NCFM and 0.63 g of insulin.	?	31 ± 28 days.
Gao *et al*, 2015[11]	*Bifidobacterium longum*, *Lactobacillus acidophilus* and *Enterococcus faecalis* (1:1:1) encapsulated with a minimum of 1.0x10^{7} UFC/g of viable cells.	Encapsulated maltodextrin.	5 days before the surgery, three times a day.
Zhang *et al*, 2012[12]	*Lactobacillus acidophilus*, *Bifidobacterium longum* and *Enterococcus faecalis* (1:1:1) encapsulated with a minimum of 1.0x10^{8} UFC/g of viable cells.	Encapsulated maltodextrin.	3 days before the surgery; the treatment group received the capsules with probiotics 3 times a day. The placebo group received maltodextrin capsules 3 times a day 3 days before the surgical procedure.
Liu *et al*, 2011[13]	*Lactobacillus plantarum* CFMCC ≥10^{11} UFC/g, *Lactobacillus acidophilus* 11 ≥7.0 x 10^{10} UFC/g and *Bifidobacterium longum* 88 5.0x10^{10} UFC/g in capsules.	Encapsulated maltodextrin and 10 g maltodextrin sachet.	16 days (6 days before the surgery and 10 days after the procedure), capsules totaling 2 g a day (2.6 x 10^{14} UFC a day).

Discussion

The results of formulations containing associations of various probiotic bacteria are justified by a synergistic mechanism that helps reduce the prevalence of *Enterobacteriaceae* bacteria such as in Liu et al[14], which used *Lactobacillus plantarum* CFMCC ≥10^{11} UFC/g, *Lactobacillus acidophilus* 11 ≥ 7.0 x 10^{10} UFC/g and *Bifidobacterium longum* 88 5.0 x 10^{10} UFC/g.

According to Rayes et al,[16] *L. plantarum* is a probiotic species that has a high adhesion capacity and colonization of the intestinal mucosa; thus, it contributes to the reduction and elimination of possible pathogenic microorganisms.

Hibberd et al[15] justified the association of *L. acidophilus* NCFM and *Bifidobacterium animalis ssp lactis* Bl-04 by the long history of both as safe and commercial use probiotics, with several documented benefits.

Gao et al[12] clarifies that the association of *Bifidobacterium longum*, *L. acidophilus* and *Enterococcus faecalis* is capable of qualitatively and/or quantitatively altering the intestinal microbiota and normalize dysbiosis; also adding that, in animal tests, *L. acidophilus* and *B. longum* showed the ability to reduce DNA damage by 12-dimethylhydrazine, a potent genotoxic.

Zhang et al[13] adds that each bacterium has greater affinity with a given intestinal region, which shows that the association of several probiotics is an interesting strategy for a better clinical result. *E. faecalis* is mainly located in the upper gastrointestinal tract, *L. acidophilus* is mainly located in the middle intestinal portion and *B. longum* is located in the lower tract.

Komatsu et al[17] clarifies that, when added in the same environment/product, probiotic cultures collaborate mutually for the growth of each other, as long as compatibility between the cultures is verified. Consequently, it was verified that *B. lactis* multiplies itself more in co-culture with *L. acidophilus*.

The same effect was verified in the co-culture of *B. bifidum* and *L. acidophilus*. This is an important fact for those who develop food products since, in addition to lactate, bifidobacteria produce acetate, which can cause an acrid sensory, limiting consumer acceptance. In the case of probiotics in the form of pharmaceutical presentations, this would improve the growth rate and reduce the fermentation time[18].

For Flesch et al[19], the association between several probiotic bacteria is interesting for increasing the host's immune response, for the activation of macrophages that increases the cytokine levels and natural killer (NK) cell activity, as well as competing for exclusion with pathogenic microorganisms by mucosal receptors, in addition to inhibiting their growth through the production of SCFA.

The association of prebiotics, such as inulin, is justified because it is a soluble fiber that serves as a substrate for the fermentation of anaerobic bacteria such as *Lactobacillus* and *Bifidobacterium*, leading to the production of lactic acid, short-chain fatty acids and other metabolites with well-documented biological activities that have proved to contribute to modulation of the intestinal microbiota, to prevention of adhesion and colonization by pathogenic bacteria, to stimulation of effective anti-inflammatory drugs and to regulation of lipid metabolism and carbohydrates. Production of these acids reduces intestinal pH and stimulates proliferation of the colon's epithelial cells[20,21].

All the articles included in this systematic review had microbiological alteration as outcome. However, each article addressed this change resorting to different methodologies.

Liu et al[14] addressed modification of the microbiota in fecal material 10 days after surgery, verifying an increase in the concentrations of *Bifidobacterium* and *Lactobacillus* (10.8 ± 0.4 CFU/g and 7.4 ± 1.0 UFC/g, respectively) in the group undergoing intervention with probiotics when compared to the control group (8.8 ± 2.4 UFC/g for *Bifidobacterium* and 6.0 ± 1.7 UFC/g for *Lactobacillus*). Microbial groups *Enterobacteriaceae* and *Candida* were also quantitatively altered in the probiotic group (6.4 ± 1.2 UFC/g and 3.1 ± 1.1 UFC/g, respectively) when compared to the control group (8.3 ± 1.0 UFC/g for *Enterobacteriaceae* and 4.7 ± 1.7 UFC/g for *Candida*).

The result presented by Liu et al[14] shows that the administration of probiotics exerts a beneficial effect on the alteration of the microbiota in the individuals who received the intervention when compared to the control group since, even 10 days after the surgery, with the use of antimicrobials necessary for surgical field prophylaxis quantification of the probiotic bacteria used, *Bifidobacterium* and *Lactobacillus*) was able to colonize the patients' GIT, at the same time that genera such as *Enterobacteriaceae* and *Candida*, which are related to pathogenic

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microorganisms and dysbiosis, had reduced counts in the group that received the intervention with probiotic bacteria.[14]

In the analysis of microbial diversity by PCR-DGGE, Liu et al[14] verified that short-term administration of the formulation containing probiotics had a positive impact on microbial variety, significantly changing the amount and diversity of the microbiota of this group in relation to the control group, showing the modulatory capacity of the intervention with probiotics[14].

Zhang et al,[13] evaluated the *Bifidobacterium* and *Escherichia coli* counts and the ratio between the two species in the feces of patients in the probiotic group (Group A) and placebo group (Group B) 6 and 3 days before the surgical procedure and at the first spontaneous postoperative defecation (which was from the 3rd to the 5th day after the surgery), verifying that, initially (6th day before the surgery), the counts were similar in both groups and that, on the 3rd day before the surgery, Group A already presented a decrease in the *E. coli* count and a significant increase in the *B. longum* count.

The results found by Zhang et al,[13] showed a beneficial effect of the preoperative administration of probiotics, which, in addition to modulating the microbiota in an inhibitory way against pathogenic microorganisms, improved the intestinal microbial *Bifidobacterium* content, which impacted on other parameters analyzed by this study and not addressed in this article, such as reduction of postoperative complications and improvement of immunohistochemical parameters.

Gao et al[12] verified changes at phylum and genus level in the mucous membrane samples of a Group of Healthy Patients (GHP), a Group of Patients with Placebo (GPP) and a Group of Patients with Probiotics (GPPr). In this paper, the most notable changes in patients subjected to the intervention with probiotics was the increase in phylum Firmicutes bacteria (66.44% in contrast to 40.21% in healthy patients and 60.97% in the placebo group) and a decrease in phylum Flavobacterium bacteria (2.18% in contrast to 8.32% in healthy patients and 1.83% in the placebo group) and Fusobacteria (1.91% in contrast to 10.08% in the placebo group and 0.01% in healthy patients).

Hibberd et al[15] also verified a significant reduction in bacteria from genus *Fusobacterium* in patients supplemented with probiotics (0.03 ± 0.05 vs. 0.81 ± 0.87) and *Peptostreptococcus* (0.04 ± 0.06 vs. 0.42 ± 0.071), two bacteria associated with CRC development. The study also showed the increase in phylum Firmicutes bacteria (*Clostridiales spp*, *Faecalibacterium*, *Eubacterium* and *Roseburia*).

Regarding the analysis of the specific microbial phyla analyzed in these two papers, Gao et al[12] observes that *Fusobacterium* constitutes less than 0.01% of the microbiota of healthy people when compared to patients with CRC (10.08% vs 0.01%), but the intervention with probiotics reduced the count of this bacterium in the group of patients with CRC that received probiotics.

The paper by Hibberd et al[12] also verified the reduction of phylum *Fusobacterium*, but also of *Peptostreptococcus*, another genus related to CRC development. The increase of phylum Firmicutes bacteria is clinically interesting, as these bacteria increase the production of butyrate, an SCFA that provides energy to the colonocytes and inhibits proliferation of cancer cells, reduces inflammation by IFN-γ and promotes cell apoptosis.

Chen et al[7] assert that *Fusobacterium* is a relevant phylotype in patients with CRC since, in addition to being associated, it is generally found in large amounts. In addition, *Bifidobacterium* is a reduced group in patients with CRC, which can predispose development of the pathology, as this bacterium genus is related to the competition of adhesion sites with pathogenetic bacteria and secrets anti-bacterial peptides in the colon.

Castellarin et al[22] adds that the mechanism that associates *Fusobacterium* with CRC is its ability to invade the bacterium since, after analyzing biopsies, extremely high amounts of RNA related to this bacterium genus were verified. In addition to that, they noticed an association of *Fusobacterium* with metastasis in lymph nodes.

Thus, Gao et al[12] assertion is shared: it is important to maintain a healthy intestinal microbiota as well bacteria diversity, as they are factors that hinder the increase of pathogenetic bacteria. The studies included showed that the association of probiotics was able to qualitatively and quantitatively change the microbiota.

Conclusion

The diverse evidence collected and analyzed on the administration and pharmaceutical formulations of *L. acidophilus* associated with other probiotic bacteria shows that these formulations have the potential to change the microbiome of patients with colorectal cancer subjected to surgical procedures, even when administration occurs in the short term and after the use of probiotics, evidencing the effect of modulating the microbiota in a health and positive way.

Despite the few studies included, the results found show a promising scenario for the use of probiotics (especially *L. acidophilus*) for application in patients with colorectal cancer. These results shows that the formulations with *L. acidophilus* have a beneficial potential to modulate the intestinal microbiota in an effective and safe way in patients with CRC and without immunosuppression, allowing the elaboration of pharmaceutical formulations for preventive and ancillary use.

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Collaborators

Conception of the project: BBF and LOF. Reviewers: BBF and LOF. Writing of the article and responsibility for all the information presented in the paper, ensuring its accuracy and integrity: BBF and LOF. Critical review and final correction: BBF and LOF. Approval of the final version: BBF and LOF.

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Conflict of interest statement

Authors declare no conflict of interest in relation to this article.

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