doi: 10.12662/2317-3206jhbs.v9i1.3783.p1-8.2021

REVIEW ARTICLE

Therapeutic potential of using probiotics in the treatment and prevention of breast câncer

Potencial terapêutico do uso de probióticos no tratamento e prevenção de câncer de mama

Tiago Soares[1], Bruna Barbosa Maia da Silva[2], Danielle Silva Araújo[1], Maria Clara Feijó de Figueiredo[1], Francisco das Chagas Leal Bezerra[1], Eliakim Aureliano da Silva[1], Ana Cibele Pereira Sousa[3], Stella Regina Arcanjo Medeiros[4], Celma de Oliveira Barbosa[5], Joilane Alves Pereira-Freire[4]

1. Discente do curso de Nutrição. Universidade Federal do Piaui (UFPI), Picos, Piaui, Brasil. 2. Discente de pós-graduação em química. Universidade Federal Rural de Pernambuco (UFRPE), Recife, Pernambuco, Brasil. 3. Docente do curso de nutrição. Centro Universitário Paraíso (UniFAP), Juazeiro do Norte, Ceará, Brasil. 4. Docente do Departamento de Nutrição. Universidade Federal do Piauí, Picos, Pi, Brasil. 5. Preceptora do curso de Nutrição. Uninassau, Teresina, Piauí, Brasil.

Abstract

Objective: This study aimed to evaluate the evidence available in the literature on probiotics on breast cancer. **Methods**: It is an integrative review of the literature, through the PICO strategy, with the guiding question “Does probiotics consumption act on oxidative stress and reduces the risk of breast cancer”? The selection of articles was made on MEDLINE, SciELO and PubMed, including those published between 2016 and january 2021, using the keywords: “breast cancer” AND “probiotics” AND “microbiota” their combinations in Portuguese and English, with previously established inclusion criteria. **Results and Discussion**: The sample consisted of ten articles, and the answers found were: scientific research in vivo and in vitro, with some variations of probiotics strains, where all demonstrate actions and/or effects on cancer cells or acted on metabolic pathways mitigating the development of tumors. **Conclusions**: The manifested potential for a possible insertion in the treatment and prevention of breast cancer, being considered an innovation for the scientific community that still fights against various types of problems related to human health, especially some types of cancers, of negative prognoses and with difficult therapeutic interventions.

Keywords: Breast cancer; Probiotic; Microbiota.

Resumo

Objetivo: Este estudo avaliou a literatura disponível sobre probióticos no câncer da mama. **Métodos**: É uma revisão integrativa da literatura, através da estratégia pico, com a pergunta orientadora "O consumo de probióticos atua sobre o stress oxidativo e reduz o risco de câncer da mama"? A seleção de artigos foi feita no MEDLINE, SciELO e PubMed, incluindo os publicados entre 2016 e janeiro de 2021, utilizando as palavras-chave: "câncer da mama" E "probióticos" E "microbiota" as suas combinações em português e inglês, com critérios de inclusão previamente estabelecidos. **Resultados e Discussão**: A amostra consistiu em dez artigos, e as respostas encontradas foram: investigação científica in vivo e in vitro, com algumas variações de estirpes de probióticos, onde todos demonstram ações e/ou efeitos sobre as células cancerosas ou atuaram sobre vias metabólicas mitigando o desenvolvimento de tumores. **Conclusões**: O potencial manifestado para uma possível inserção de probióticos no tratamento e prevenção do câncer da mama, sendo considerado uma inovação para a comunidade científica que ainda luta contra vários tipos de problemas relacionados com a saúde humana, especialmente alguns tipos de câncer de prognósticos negativos e com intervenções terapêuticas difíceis.

Palavras-chave: Câncer de mama; Probióticos; Microbiota.

INTRODUCTION

Probiotics are living micro-organisms which, when administered in appropriate amounts, either in the form of food or in the form of a food supplement provides various benefits to the health and well-being of the individual host[1].

The market for probiotics is constantly growing due to factors such as greater awareness of one's own health on the part of consumers seeking food and products that have high nutritional and therapeutic value. In this context, probiotics have been a source of studies and application in the food and pharmaceutical industry due to the enormous benefits that promote the health of those who consume them, such as improved immunological function, intestinal flora, besides being able to inhibit the proliferation of pathogenic bacteria[2].

The main beneficial effects on human health caused by probiotics are constantly described in the scientific literature, among them are: prevention of urogenital infections, immunomodulatory functions, control of serum cholesterol, blood pressure and gestational diabetes, relief of allergic symptoms and lactose intolerance, reduction of gastrointestinal disorders such as intestinal inflammatory syndromes, and prevention against

Correspondence: Joilane Alves Pereira Freire. Universidade Federal do Piauí, Picos, Pi, Brasil. E-mail: joilane@hotmail.com
Conflict of interest: The authors declare that there is no conflict of interest.
Received: 2020 Mar 5; Revised: 2021 Jun 17; Accepted: 2021 Jul 22

certain types of cancer[2-9].

The preventive effects of probiotics against the development of cancer can be mediated by various mechanisms, such as alteration of the gastrointestinal microbiota, improvement in the immune response of the host, anti-proliferative, cytotoxic and antioxidant activity, these help to avoid the effects caused by reactive oxygen species (ROS), and stimulate the induction of apoptosis. Several recent studies in vivo, in vitro, in humans and epidemiological demonstrate beneficial functions of probiotic strains against cancer cells in colon, bladder, liver, gastric and breast cancer[10-17].

Breast cancer, specifically, is a pathology characterized by uncontrolled proliferation of cells present in the breast, a process that results in the formation of a tumor[18]. According to the World Health Organization (WHO), breast cancer is the most common malignant cancer that causes the death of adult women and the second most common cancer worldwide, accounting for a total of 24.2% of cases in 2018, and is a significant public health problem in both developed and developing countries[19-21].

In Brazil, this pathology is the most incident among the female public of all regions, except for non-melanoma skin cancer. It is estimated that in each year of the triennial (2020-2022) there will be approximately 66,280 new cases, corresponding to 61.61 new cases for every 100,000 women. It is observed an increase in these values when compared to the 2019 estimate of 59,700 new cases and the rate of 56.33 per 100,000 women[22].

Some epidemiological parameters such as incidence, mortality rate and survival related to this disease present several differences between countries and regions, which may be due to the healthy habits and diets characteristic of each site[23-24]. It is known that several factors in common were identified as causing the increased risk of developing breast cancer, they are: family or personal history of breast cancer, the use of oral contraceptive, obesity, inadequate eating habits, menopause after 50 years, mutations in the genes BRCA1 and BRCA2 among others[25-26].

The stage at which the tumor is diagnosed influences the strategies chosen for the treatment scheme. Currently, the protocols use an approach that includes surgical procedures, targeted therapy, chemotherapy, endocrine and radiotherapy[28-27]. However, despite major technological advances in both diagnosis and therapy, breast cancer mortality remains high around the world, leading to a continuous search for new methods and strategies to manage this pathology, such as the use of functional foods[13-14].

As already mentioned, probiotics can be useful in the prevention or treatment of breast cancer, however, it should be emphasized that new research should be carried out to make it possible to explore and understand all the mechanisms, be they metabolic, immune and molecular, that surround this topic[12]. Given the above, the objective of the present work was to verify through the literature the effect of probiotics on breast cancer.

METHODS

This is an integrative review of the literature, to analyze existing research related to the guiding question: Does the consumption of probiotics act on oxidative stress and reduces the risk of breast cancer? It is notorious that this type of research is important, because from the production of contents and construction of data through integrative revision, the delimitation for the choice of research problems and the search for new lines of investigation also provide the identification of theories and hypotheses related to it[15].

The performance of bibliographic research is one of the best ways to start a study, looking for similarities and differences between the articles raised in the reference documents. The compilation of information in electronic media is an important advance for researchers, democratizing access and allowing the scope of updating[21].

The integrative review of the nutrition literature can enhance knowledge formation based on informed studies so that professionals in the field consistently assist. This method makes it possible to trace strategies and know the evolution of the studies over time confirming possible evidence of the subject being worked on[29].

The data collection was carried out through a search in the MEDLINE (International Health Sciences Literature), SciELO (Scientific Electronic Library Online) and PubMed databases, having as inclusion procedure the use of original articles available in full, online, with qualitative or quantitative approach, in Portuguese and English languages with publication in the period from 2016 to January 2021, from the Health Sciences Descriptors (DECS): “breast cancer” AND “probiotics” AND “microbiota” their combinations in Portuguese and English. The exclusion criteria used were: review articles and experience reports; articles published more than five years ago that do not satisfy the descriptors evidenced (Table 1).

Table 1. Description of the PICO strategy.

Initials	Description	Analysis
P	Patient / problem	Breast cancer patient
I	Intervention	Probiotic consumption
C	Comparison / control	Healthy people
O	Result / outcome	Improvement or influence in breast cancer treatment

Source: Developed by the authors themselves.

The elaboration of the research question was based on the PICO strategy which represents an acronym: P - patient/problem; I - intervention; C - comparison/control; O - result/disclosure is a tool used by the practice based on scientific evidence, to assist in the bibliographic survey seeking to solve problems of care practice, teaching and research[30,31], according to (Table 1).

1,572 studies were identified using the descriptors (breast cancer AND probiotics AND microbiota) and the search strategies used in the respective databases led to the number of articles presented in (Table 2).

Table 2. Number of studies identified in the databases (n=1.572), included in the integrative review, Picos-PI, Brazil, 2020.

Database	Num. of studies (n=1.572)
MEDLINE	1
SciELO	1
PubMed	8

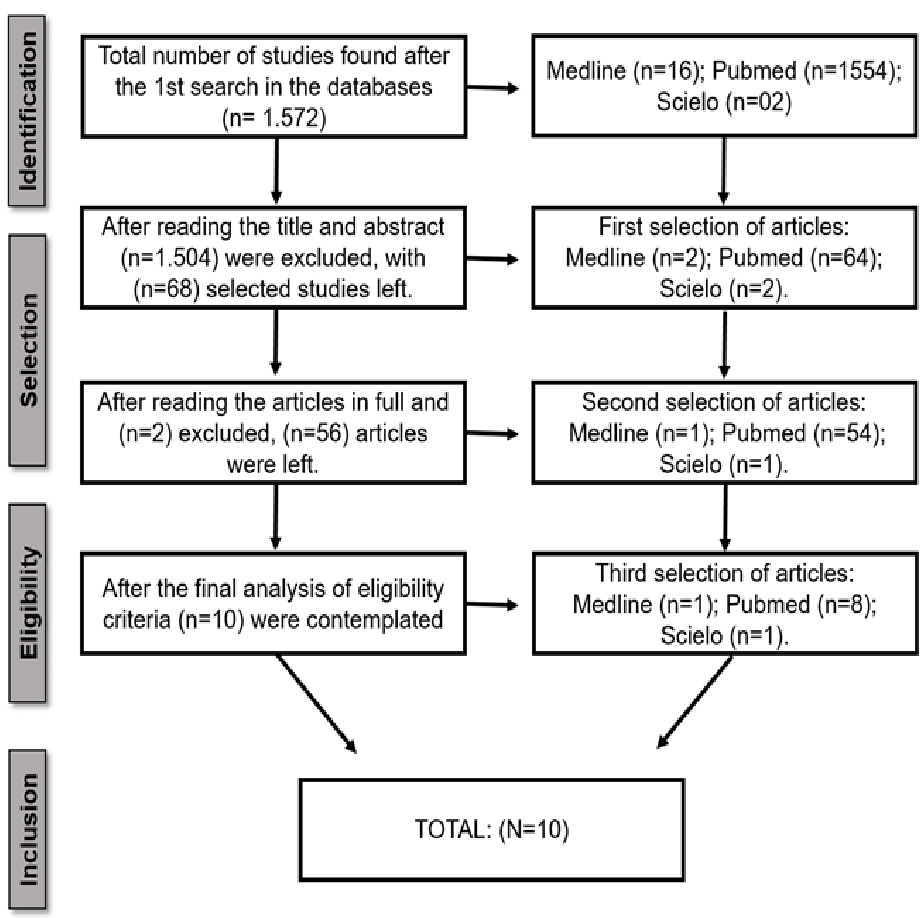
Source: Developed by the authors themselves.

After reading the 68 pre-selected studies, 56 were excluded and the sample of the present review consisted of ten primary studies that fit the eligibility rules as shown in the organization chart illustrated in (Fig. 1), in which the search strategies used in the respective databases and the reasons for exclusion were highlighted, as recommended by the PRISMA protocol[32,33].

RESULTS AND DISCUSSION

In the bibliographic search, 1572 articles were found using the descriptors (breast cancer AND probiotics AND microbiota), which soon after passing through selection criteria, ten articles were elected that fit the eligibility norms as shown in the organization chart (Fig. 1). The ten articles selected to compose this work were from international journals published in English, available in the databases Pubmed, Medline and Scielo, which were the only ones that demonstrated results with the defined descriptors and the characterization of the chosen articles were exposed in (Table 1).

Figure 1. Search organization chart and selection of articles, according to eligibility criteria.



Studies involving probiotics in the treatment and prevention of breast cancer are considered an innovation for the scientific community that still fight against several types of problems related to human health, therefore in (Chart 1) are detailed original articles from the last five years, where the authors developed in vivo and in vitro scientific research, recording the potential activity of the following probiotics respectively: *Faecalibacterium prausnitzii, Kefir, Lactobacillus crispatus, Lactobacillus plantarum, Lactobacillus fermentum, Lactobacillus plantarum Lactobacillus Brevis, Lactobacillus pentosus, Lactobacillus acidipiscis, Kombucha, Chorella vulgaris, Enterococcus faecalis e Staphylococcus hominis*

Chart 1. Characterization of the main results found regarding the performance of probiotics in cancer cells present in the breast.

PROBIOTIC	REFERENCE	RESULTS/FINDINGS
Faecalibacterium prausnitzii (in vitro).	(24)	The best known species of the genus Faecalibacterium prausnitzii inhibited the IL-6 / STAT3 route in breast cancer cells. The analysis of the difference between the case group and the control group showed that *Faecalibacterium was significantly* reduced in patients with breast cancer compared to the normal group.
Kefir Water. (in vitro and in vivo).	(27)	The 4T1 cancer cells collected from the rats were treated with kefir water in vitro and the BALB / c rats were orally treated with kefir water. The kefir water was cytotoxic to 4T1 cells with values in IC_{50} (half of the maximum inhibitory concentration) after 48 and 72 hours of 12.5 and 8.33 mg/mL respectively. The tumor presented significant reduction in size and weight. In the group treated with kefir water there was an increase in auxiliary T cells (5 times) and cytotoxic T cells (7 times), as well as in pro-inflammatory and pro-angiogenic markers.
Lactobacillus crispatus (in vivo)	(30)	40 BALB / c mice received the cellular line of breast cancer4T1, and were exposed to a treatment with intraperitoneal injections of L. *crispatus* in different concentrations. It was observed that in the experimental group treated with the concentration of 1×10^8 bacteria / 200 µl, the tumor size was reduced resulting in improved survival and decreased Cox2 expression of tumor tissues. In addition, arginase and iNOS expressions increased in the spleen and tumor tissues of patients treated with 5×10^8 bacteria / 200 µl.
Lactobacillus plantarum associated with prebiotic inulin and melatonin (in vivo)	(31)	Daily administration of probiotic (PRO), prebiotic (PRE) and melatonin (MEL) lasted 16 weeks and was started 14 days before the first dose of N-nitroso-N-methylurea (NMU), the direct-acting carcinogen. The growth of the tumor was not altered, however, there was a marked reduction in the proportion of high- and low-grade carcinomas and in the tumor expression of Ki-67 after treatment with PRO+PRE; melatonin increased these effects. The combination PRO + PRE + MEL improved tumor infiltration in CD4+ and CD8+ T-cells induced by PRO/PRE and increased CD25+FoxP3+ regulatory T-cells in tumors.
Lactobacillus fermentum and Lactobacillus plantarum combined with nanoparticles of fluorescent cadmium sulphide (in vitro)	(5)	A gradual decrease in MCF-7 cell activity was observed after treatment with CdSNPs, where almost 80% of the cells did not survive a concentration of 5 ppm of CdSNPs after 24 h and almost zero survival was observed after 48 h of incubation. There was a decrease in cell viability after treatment with microbots, *Lactobacillus* spp. alone and Lactobacillus spp. with externally supplemented NdCdS. However, microbial infection showed maximum efficacy compared to other bacterial infections in 2 h of incubation.
Lactobacillus Brevis isolated and in association with tamoxifen (In vitro)	(40)	Lactobacillus Brevis (LBS) in combination with tamoxifen (TMX) was used as treatment. The results indicated that LBS induces apoptosis in MCF-7 in high concentrations. The transcription of Bcl-2 was reduced, but the expression of Bax mRNA was improved. The TMX inhibitory effect on cell growth was synergistically increased by LBS. Furthermore, the levels of Bcl-2 mRNA in cells exposed to TAM/LBS were lower than in those treated with TAM only.
Lactobacillus pentosus and Lactobacillus acidipiscis	(1)	The results showed that the two strains of Lactobacillus had good anti-proliferative effects against the two lines of cancer cells, breast (MDA-MB-231) and liver (HepG2), while their effects on normal cells were weak. According to antioxidant tests the two strains of L*actobacillus* demonstrated more than 135 and less than 50 µg trolox / mL of antioxidant activity, showing the potential of the strains as possible probiotics for humans.
Kombucha alone or with ginger (in vivo)	(32)	The kombucha with and without the ginger were administered to the BALB / c mice before and after induction of the tumor. Superoxide dismutase (SOD), catalase, glutathione (GSH) and malondialdehyde (MDA) were evaluated in tumors, liver and kidneys. The administration of ginger tea with kombucha reduced the catalase activity as well as the level of GSH and MDA in the tumor homogenate ($p < 0.001$). And it could be observed that in the kidney that received the kombucha tea there was a decrease in SOD activity and an increase of MDA ($p < 0.01$).
Chorella vulgaris (In vivo)	(34)	Bald mice received daily *Chorela Vulgaris* powder (CV) for 42 days (control group, CV 200 and CV 300 mg per kg of weight). On day 14 they received the tumor model where every five days volume and weight of the tumor were monitored, on day 43 blood, spleen, lungs, and tumor tissue were collected. There was significant growth in volume of the CV200 tumor compared to the control group ($p = 0.047$). No significant difference between the Control and CV300 groups.

PROBIOTIC	REFERENCE	RESULTS/FINDINGS
Enterococcus faecalis and Staphylococcus hominis (In vitro)	(7)	The forms of these bacteria, killed by heat and cytoplasmic fractions caused a decrease in the MCF-7 carcinogenic model of (up to 33.29%) cellular proliferation in concentration and time dependent manner. The morphological characteristics by flow cytometry analysis suggested that about 34.60% of the treated MCF-7 was in apoptosis. A strong anti-proliferative activity was efficiently induced through the sub-G1 accumulation (up to 83.17%) in the treated MCF-7 and decrease in the G0 / G1 phase (74.39%). MCF-10A cells treated with both bacteria showed no significant difference with the untreated (> 90% viability).

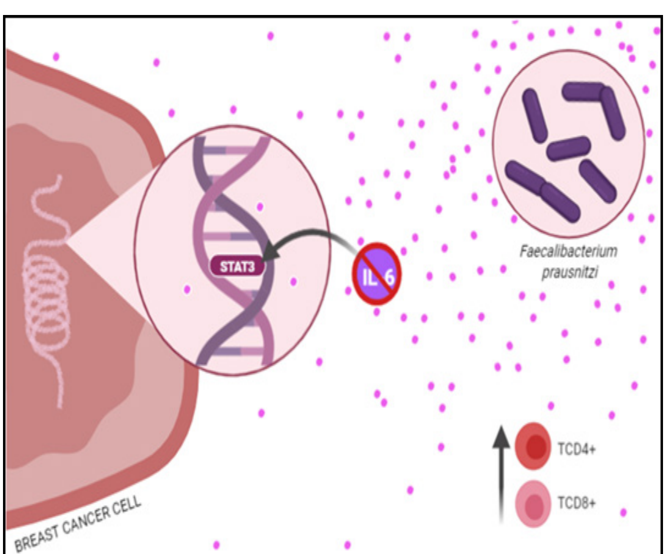
Source: Developed by the authors themselves.

Faecalibacterium prausnitzi: anti-inflammatory and antitumor action

According to Martín et al. this microorganism is considered a gram-positive bacterium, extremely sensitive to oxygen, which composes the human fecal microbiota, belongs to the Clostridium group, of the *phylum Firmicutes*, class *Clostridia* and family of *Ruminococcaceae. F. prausnitzii* produces anti-inflammatory metabolites that help the vitality of the intestine, as well as, are responsible for the synthesis of butyrate, a short chain fatty acid, which has action in the repair of the colonic epithelium and synthesis of Treg cells[35,40].

Researchers such as Ma and collaborators[34,36] pointed out that the probiotic *F. prausnitzii*, the best known species of the genus *Faecalibacterium*, produced an inhibitory effect in the secretion pathway of interleukin-6 (IL-6) and phosphorylation of Janus kinase 2 (JAK2), being them signal transducers and activators of transition 3 (STAT3) in breast cancer cells, showing that studies involving the production or modulation of STAT3 are indispensable, since the serum levels of this protein in its active form are linked to the growth of tumor cells, bringing a poor clinical prognosis for the patient, besides stimulating the resistance of the tumor to chemotherapy treatments.

Figure 2. Representation of inhibition of Interleukin-6 (IL-6) being it a signal transducer for STAT3, by the microorganism *Faecalibacterium prausnitz*



Source: Developed by the authors using the BioRender.com program.

Kefir water: an effective agent in cancer treatment and prevention?

Kefir is a traditional drink made from the fermentation of kefir grains associated with various substrates, cow's milk being the most widely used. However we can see that the fermented beverage from kefir grains is also made with the use of water kefir, being the same a fermented beverage composed of the kefir grains of water (the inoculum) associated with water, fruits (dry) and sugar. Kefir grains contain various types of microbial flora, including the most commonly studied species with probiotic potential, such as *Lactobacillus acidophilus, Lactobacillus casei and Lactococcus lactis subsp Lactis*[40].

Grains are a mixture of yeasts and lactic acid bacteria within a polysaccharide and protein matrix, in a symbiotic community. According to Fels et al (2018) the main ingredients of kefir are lactic acid, ethanol and CO_2. The components of the kefir complex are involved in the synthesis of anti-cancer bioactive components, including peptides, polysaccharides and sphingolipids, playing vital roles in different signaling pathways and biological cellular processes such as apoptosis, proliferation and transformation. Therefore, kefir can act as an effective agent in the treatment and prevention of cancer[33].

Zamberi and collaborators[25] conducted a study on the anti-metastatic and antiangiogenic effects of Kefir water in murine breast cancer cells and noted that the probiotic showed cytotoxic activity with an inhibitory concentration of half the maximum (IC_{50}) of 12.5 and 8.33 mg/ml for 48 hours and 72 hours respectively in 4T1 cells. The tumor size in mice treated with kefir water was smaller than those who did not receive the therapy. The weight and volume of the tumor were also significantly reduced by 29.53% and 32.92%. The levels of cytokines related to tumor growth (IL-10 and IL-1β) decreased significantly in the group that used Kefir water, on the other hand, the levels of cytokines related to immunomodulation (IFN-γ and IL-2) increased significantly. The significant reduction in cellular migration and invasion in treated cells demonstrated the potency of water kefir as an anti-metastatic agent.

Lactobacillus spp.

Among the studies (Table 1), it was observed that different authors chose to use species of *Lactobacillus*, since these gram positive and lactic acid producing microorganisms are widely used in the composition of probiotics, moreover, they allow easy access associated with their occurrence in several microbiomes associated with man, covering intestinal, vaginal, oral and cutaneous communities, as well as food and animal tissues[37,38].

In the study conducted by Motevaseli and collaborators[39], *Lactobacillus crispatus* injected intra-peritoneously in mice was used, where it brought good results regarding the reduction of tumor size, expression of COX2, arginase and INOS, on the other hand, Kassayová[26] associated *Lactobacillus plantarum* with prebiotic inulin and melatonin in the diet of the mouse. The study was initiated 14 days before the first dose of N- nitroso-N-methylurea (NMU), a direct-acting carcinogen, and lasted 16 weeks. Although tumor growth is not, a marked reduction in the proportion of high/low degree carcinomas and in Ki-67 tumor expression was found after treatment with PRO+PRE; the addition of melatonin was able to potentiate the local immune response induced by the combination of probiotics and prebiotics in breast tumor tissue, this promising combination needs to be evaluated in future clinical studies.

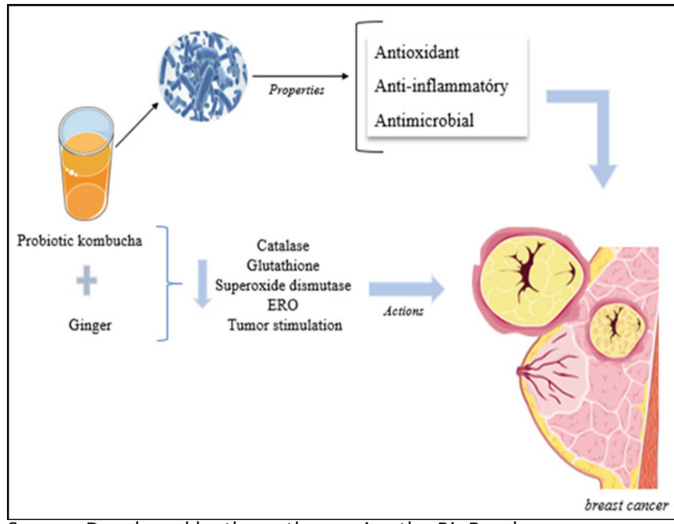
In addition, in 2017, Raj and Das developed an in vitro research with these microorganisms, but tests another type of therapy, this in turn, analyzes the capacity of biosynalization of the preparation of *L. fermentum* and *L. plantarum* with nanoparticles of fluorescent cadmium sulphide, as well as the direct toxicity in neoplastic cells of breast cancer. Relating the cytotoxicity Shokryazdan et al (2018) tested strains of *Lactobacillus pentosus* and *Lactobacillus acidipiscis* in breast and liver cancer cells, where both showed good antiproliferative activity[10]. In addition, other researches were carried out with *Lactobacillius*, as an example, Nasiri and collaborators associated L. Brevis with tamoxifen, an antineoplastic drug used in the pharmacotherapy of patients with breast cancer, thus it was noted that the probiotic acted synergistically with the drug, increasing the effectiveness of chemotherapy in reducing the size of the tumor.

Kombucha

Villarreal-soto et al (2018) emphasizes properties that the kombucha has, being characterized as a drink derived from the fermentation of teas that has antioxidant, anti-inflammatory, antimicrobial and probiotic properties that can positively alter cancer[27]. Salafzoon et al (2017) in their study treats innovatively the antioxidant actions of kombucha isolated and associated with ginger, in *in vivo* studies, in different types of tumors in breast cancer[18].

This drink, when associated with ginger, becomes rich in bioactive compounds with antitumor properties, which will contribute to the inhibition of tumor stimulation. The reduction in the levels of catalase, GSH (Glutathione), MDA and SOD (superoxide dismutase) provoked by the administration of kombucha tea with ginger, may be useful in the reduction of the overproduction of reactive oxygen species, characteristic of cancer. Besides, the increase of the catalase levels caused by the administration of the isolated kombucha, indicates the possibility of lesser antioxidant impacts in the body[38].

Figure 3: Mechanism of action of kombucha associated with ginger in breast cancer.



Source: Developed by the authors using the BioRender.com program.

Chlorella vulgaris

In their study, Khalilnezhad et al. (2018) observed that the administration of 200mg/kg dose of Chlorella vulgaris (CV) in mice facilitated breast tumor growth, when compared to mice that received 300mg/kg of CV35. Moreover, he also noted that the effect of CV dosage could not be analyzed separately, as several other factors are involved in the tumor growth scenario, such as pro-inflammatory cytokines, immunoglobulins, alteration of immune system cells and growth factors, which when associated with the administration of different amounts of *Chlorella vulgaris*, can stimulate or inhibit carcinogenic activity. Furthermore, in this same study, it was observed the possibility of interaction between the dosages of *Chlorella vulgaris* administered with intra-tumor factors, such as IL-4 and IL-17, which may act potentiating the increase of the tumor. The incorporation of microalgae into probiotic fermented milks along with enhancing the viability of probiotics would increase their functional characteristic[41].

Enterococcus faecalis

Enterococcus faecalis is a Gram-positive bacterium of the human gastrointestinal tract and other mammals which is responsible for urinary infections and meningitis[32]. The research approached by Hassan et al (2016), proved the bacterial activity in the epithelial cell line of the non-malignant breast, the bacteria cause a significant decrease in cell proliferation of up to 33.29% according to the concentration and time variables[31]. It was also observed that MCF-10 cells treated with both bacteria did not show significant differences between the treated and untreated group (> 90% viability).

On the anti-tumor effect, Gu et al (2017) contributed demonstrating that the *Enterococcus faecalis* orally administered in the growth of Ehrlich solid carcinoma cells in mice during 34 days of oral administration (200 mg / kg body weight) resulted primarily in the suppression of 83.1% in tumor size (p <0.01), thus showing above all that this probiotic can have effective anti-tumor action[22].

Staphylococcus hominis

In turn, it is a gram-positive bacteria commonly found in human skin, responsible for body odor. The mechanisms with pathogenic effects of *S. hominis* have not yet been determined. These microorganisms are known as potentially opportunistic pathogens and can cause several infections in the bloodstream, endocarditis, peritonitis, osteomyelitis, bone and joint infections[14].

Hassan et al (2016) conducted a pioneering research using *S. hominis* for activity in breast cancer cells, it compared the bacteria with *E. faecalis*, and it was observed that *S. hominis* showed higher cytotoxicity in all forms of the bacteria used in tests with breast adenocarcinoma cells[21]. On the other hand, the cytotoxicity pattern produced by *E. faecalis* showed more safety in terms of dose and time. *E. faecalis* and *S. hominis* caused a significant decrease in the proliferation of human breast cancer cells. Concentrations and time greatly influence the cytotoxicity of these bacteria.

CONCLUSIONS

The integrative review made possible the synthesis and elucidation of the main beneficial effects provided by the described probiotics, such as anti-tumor, antioxidant, antineoplastic, anti-inflammatory activity, control of gastrointestinal disturbances, besides the production of vitamins, short chain fatty acids and microorganisms that will act positively in the organism, including positive alterations in the metabolism of cardio metabolic and tumor cells.

Thus, it was possible to demonstrate that the consumption of probiotics can act in the process of oxidative stress and reduction of the risks of breast cancer, and can act as important supports in the prevention, pharmacological or non-pharmacological treatment of breast cancer. Therefore, it is necessary to conduct more clinical studies that evaluate the beneficial and potential therapeutic effects of the use of probiotics, clearly analyzing the mechanisms of action, isolated effects, and also their influences on the different organs and metabolic pathways.

REFERENCES

1. Park S, Kang J, Choi S, Park H, Hwang E, Kang YG, et al. Cholesterol-lowering effect of Lactobacillus rhamnosus BFE5264 and its influence on the gut microbiome and propionate level in a murine model. PLoS One. 2018 Aug; 13(8): e0203150. doi: 10.1371/journal.pone.0203150.

2. Vitellio P, Celano G, Bonfrate L, Gobbetti M, Portincasa P, De Angelis M. Effects of Bifidobacterium longum and Lactobacillus rhamnosus on gut microbiota in patients with lactose intolerance and persisting functional gastrointestinal symptoms: a randomised, double-blind, cross-over study. Nutrients. 2019 Apr; 11(4): 886. doi: 10.3390/nu11040886.

3. Shokryazdan P, Jahromi MF, Bashokouh F, Idrus Z, Liang JB. Antiproliferation effects and antioxidant activity of two new Lactobacillus strains. Braz. J. Food Technol. 2018; (21): 1-8. doi: https://doi.org/10.1590/1981-6723.6416.

4. Chuah LO, Foo HL, Loh TC, Alitheen, NBM, Yeap SK, Mutalib NEA, Yusoff K. Postbiotic metabolites produced by Lactobacillus plantarum strains exert selective cytotoxicity effects on cancer cells. BMC Complement Altern Med. 2019 Jun; 19(1): 114. doi: 10.1186/s12906-019-2528-2.

5. Ren Q, Yang B, Zhu G, Wang S, Fu C, Zhang H, Ross RP, Stanton C, Chen H, Chen W. Antiproliferation activity and mechanism of c9, t11, c15-CLNA and t9, t11, c15-CLNA from Lactobacillus plantarum ZS2058 on colon cancer cells. Molecules. 2020 Mar; 25(5):1225. doi: 10.3390/molecules25051225.

6. Seow SW, Rahmat JN, Kanakkappillai Mohamed AA, Mahendran R, Lee YK, Bay BH. Lactobacillus species is more cytotoxic to human bladder cancer cells than Mycobacterium bovis (bacillus Calmette-Guerin). J Urol. 2002 Nov; 168(5): 2236–2239. doi: 10.1097/01.ju.0000034353.97729.69.

7. Ma J, Sun L, Liu Y, Ren H, Shen Y, Bi F, et al. Alter between gut bacteria and blood metabolites and the anti-tumor effects of Faecalibacterium prausnitzii in breast cancer. BMC Microbiol. 2020; 20: 1-19.

8. De Cicco P, Catani MV, Gasperi V, Sibilano M, Quaglietta M, Savini I. Nutrition and breast cancer: a literature review on prevention, treatment and recurrence. Nutrients. 2019 Jul; 11(7):1514. doi: 10.3390/nu11071514.

9. Porter P. “Westernizing” women’s risks? breast cancer in lower-income countries. N. Engl J Med. 2008 Jan; 358(3): 213–216. doi: 10.1056/NEJMp0708307.

10. Silva JAG. National Cancer Institute. The situation of breast cancer in Brazil: synthesis of data from information systems. Rio de Janeiro: INCA; 2019.

11. Lopes CM, Dourado A, Oliveira R. Phytotherapy and nutritional supplements on breast cancer. BioMed Res Int. 2017; 2017: 7207983. doi: 10.1155/2017/7207983.

12. McCullough ML, Gapstur SM, Shah R, Campbell PT, Wang Y, Doyle C, Gaudet MM. Pre- and postdiagnostic diet in relation to mortality among breast cancer survivors in the CPS-II Nutrition Cohort. Cancer Causes Control. 2016 Nov; 27(11):1303-1314. doi: 10.1007/s10552-016-0802-x.

13. Parida S, Sharma D. Microbial alterations and risk factors of breast cancer: connections and mechanistic insights. Cells. 2020 Apr; 9(5): 1091. doi: 10.3390/cells9051091.

14. Eslami-S Z, Majidzadeh-A K, Halvaei S, Babapirali F, Esmaeili R. Microbiome and breast cancer: new role for an ancient population. Front Oncol. 2020; 10: 120. doi: 10.3389/fonc.2020.00120.

15 Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep; 26(Suppl): v8–v30. doi: 10.1093/annonc/mdv298.

16. Mendoza L. Potential effect of probiotics in the treatment of breast cancer. Oncol Rev. 2019 Jul; 13(2): 134-138. doi: 10.4081/oncol.2019.422.

17. Bento AV. How to do a literature review: theoretical and practical considerations. Rev JA 2012; 65(7): 42-44.

18. Souza MT, Silva MD, Carvalho R. Integrative review: what it is and how to do it. Einstein. 2010 Jan-Mar; 1(8): 102-106. doi: https://doi.org/10.1590/S1679-

45082010RW1134.

19. Botelho LLR, Cunha CCA, Macedo M. O método da revisão integrativa nos estudos organizacionais. Gestão Soc. 2011; 11(5): 121-136. doi: https://doi.org/10.21171/ges.v5i11.1220

20. Santos CMC, Pimenta CADM, Nobre MRC. The PICO strategy for the research question construction and evidence research. Rev Latino-am de Enfermagem. 2007 JUn; 15(3): 508-511. doi: https://doi.org/10.1590/S0104-11692007000300023.

21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 2015 Jan; 4(1): 1-9. doi: 10.1186/2046-4053-4-1.

22. Martín R, Bermúdez-Humarán LG, Langella P. Searching for the bacterial effector: The example of the multi-skilled comensal bacterium Faecalibacterium prausnitzii. Front Microbiol. 2018 Mar; (9): 346. doi: 10.3389/fmicb.2018.00346.

23. Ferreira-Halderm CV, De Sousa AVF, Andradem SS. Action and function of Faecalibacterium prausnitzii in health and disease. Best Pract Res Clin Gastroenterol. 2017 Dec; 31(6): 643-648. doi: 10.1016/j.bpg.2017.09.011.

24. Ma J, Sun L, Liu Y, Ren H, Shen Y, Bi F, et al. Alter between gut bacteria and blood metabolites and the anti-tumor effects of Faecalibacterium prausnitzii in breast cancer. BMC microbiol. 2020 Apr; (20): 1-19.

25. Johnson DE, O´keefe RA, Grandis JR. Targeting the IL- 6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol. 2018 Apr; 4(15): 234-248. doi: 10.1038/nrclinonc.2018.8.

26. Chen YT, Lin YC, Lin JS, Yang NS, Chen MJ. A cepa de kefir açucarada Lactobacillus mali APS1 melhorou a esteatose hepática pela regulação de SIRT-1 / Nrf-2 e da microbiota intestinal em ratos. Mol Nutr Food Res. 2018; 62(8): 1700903.

27. Laureys D, De Vuyst L. The water kefir grain inoculum determines the characteristics of the resulting water kefir fermentation process. J Appl Microbiol. 2017 Mar; 122(3): 719-732. doi: 10.1111/jam.13370.

28. Fels L, Jakob F, Vogel RF, Wefers D. Structural characterization of the exopolysaccharides from water kefir. Carb Polymers. 2018 Jun; 189: 296-303. doi: https://doi.org/10.1016/j.carbpol.2018.02.037.

29. Brandt K, Barrangou R. Using glycolysis enzyme sequences to inform Lactobacillus phylogeny. Microb Genom. 2018 Jun; 4(6): e000187. doi: 10.1099/mgen.0.000187.

30. Motevaseli E, Khorramizadeh M, Hadjati J, Bonab S, Eslami S, Ghafouri-Fard S. Investigation of antitumor effects of Lactobacillus crispatus in experimental model of breast cancer in BALB/c mice. Immunotherapy. 2018 Feb; 10(2): 119–129. doi: 10.2217/imt-2017-0088.

31. Kassayova M, Bobrov N, Strojný L, Orendáš P, Demečková V, Jendželovský R, et al. Anticancer and immunomodulatory effects of Lactobacillus plantarum LS/07, inulin and melatonin in NMU-induced rat model of breast cancer. Anticancer Res. 2016 Jun; 6(36): 2719-2728.

32. Villarreal-Soto SA, Beaufort S, Bouajila J, Souchard JP, Taillandier P. Understanding Kombucha Tea Fermentation: A Review. J Food Sci. 2018 Mar; 83(3): 580-588. doi: 10.1111/1750-3841.14068.

33. Salafzoon S, Hosseini HM, Halabian R. Evaluation of the antioxidantimpact of ginger-basedkombuchaon the murine breast cancer model. J Complement Integr Med. 2017 Oct; 15(1): /j/jcim.2018.15.issue-1/jcim-2017-0071/jcim-2017-0071.xml. doi: 10.1515/jcim-2017-0071.

34. Khalilnezhad A, Mahmoudian E, Mosaffa N, Anissian A, Rashidi M, Amani D. Effects of Chlorella vulgaris on tumor growth in mammary tumor-bearing Balb/c mice: discussing association of an immunesuppressed protumor microenvironment with serum IFNγ and IgG decrease and spleen IgG potentiation. Eur. J. Nutr. 2018 Apr; 57(3): 1025-1044. doi: 10.1007/s00394-017-1387-1.

35. Barros J, Melo LD, Poeta P, Igrejas G, Ferraz MP, Azeredo J, Monteiro FJ. Lytic bacteriophages against multidrug-resistant Staphylococcus aureus, Enterococcus faecalis and Escherichia coli isolates from orthopaedic implant-associated infections. Int J Antimicrob Agents. 2019 Sep; 3(54): 329-337. doi: https://doi.org/10.1016/j.ijantimicag.2019.06.007.

36. Hassan Z, Mustafa S, Rahim RA, Isa NM. Anti-breast cancer effects of live, heat-killed and cytoplasmic fractions of Enterococcus faecalis and Staphylococcus hominis isolated from human breast milk. In Vitro Cell Dev Biol Anim. 2016 Mar; 52(3): 337-348. doi: 10.1007/s11626-015-9978-8.

37. Gu YH, Choi H, Yamashita T, Kang KM, Iwasa M, Lee MJ, et al. Produção farmacêutica de β-glucanos Enterococcus faecalis-2001 antitumoral e imuno-potenciadora: atividade aumentada de macrófagos e linfócitos em camundongos implantados em tumores. Atual biotec farmac. 2017; 18(8): 653-661.

38. Frickmann H, Hahn A, Skusa R, Mund N, Viehweger V, Köller T, Podbielski A. Comparison of the etiological relevance of Staphylococcus haemolyticus and Staphylococcus hominis. Eur J Clin Microbiol Infect Dis. 2018 Aug; 37(8):1539-1545. doi: 10.1007/s10096-018-3282-y.

39. Szczuka E, Krzymińska S, Bogucka N, Kaznowski A. Mecanismos multifatoriais da patogênese de Staphylococcus hominis resistente à meticilina isolado de infecções da corrente sanguínea. Ant van Leeuw. 2018; 111(7): 1259-1265.

40. Nasiri Z, Montazeri H, Akbari N, Mirfazli SS, Tarighi P. Synergistic cytotoxic and apoptotic effects of local probiotic Lactobacillus brevis isolated from regional dairy products in combination with tamoxifen. Nutr Cancer. 2021; 73(2): 290-299. doi: 10.1080/01635581.2020.1743871.

41. Beheshtipour H, Mortazavian AM, Mohammadi R, Sohrabvandi S, Khosravi-Darani K. Supplementation of Spirulina platensis and Chlorella vulgaris algae into probiotic fermented milks. Comp Rev Food Scienc Food Saf 2013 Mar; 12: 144-154.

Como citar este artigo/ How to cite this article:
Soares T, Silva BBM, Araújo DS, Figueiredo MCF, Bezerra FCL, Silva EA, et al. Therapeutic potential of using probiotics in the treatment and prevention of breast câncer. J Health Biol Sci. 2021; 9(1):1-8.