Probiotics and Probiotic-like Agents against Chemotherapy-Induced Intestinal Mucositis

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Cancer chemotherapy has allowed many patients to survive, but not without risks derived from its adverse effects. Drugs, such as 5-fluorouracil, irinotecan, oxaliplatin, methotrexate, and others, as well as different drug combinations trigger intestinal mucositis that may cause or contribute to anorexia, pain, diarrhea, weight loss, systemic infections, and even death. Dysbiosis is a hallmark of chemotherapy-induced intestinal mucositis and diarrhea, and, therefore, strategies aimed at modulating intestinal microbiota may be useful to counteract and prevent those dreadful effects.

chemotherapy mucositis probiotic synbiotic paraprobiotic postbiotic

1. Introduction

Currently, one of the main causes of death in the world is the development of different types of cancer. According to data provided by the Global Cancer Observatory [1], 19.3 million cases of cancer were diagnosed in 2020, and 9.96 million deaths occurred because of this disease. In addition, aspects associated with the current lifestyle such as diet, high consumption of ultra-processed foods, sedentary lifestyle, alcohol consumption, or smoking are significantly increasing the risk of suffering cancer [2]. For these reasons, in the forthcoming years, these statistics are expected to increase [1]. Fortunately, early detection and the advances in cancer treatments, make the survival rate of patients higher. However, these treatments have important side effects on patients, which can sometimes be highly limiting in their daily lives and, if not properly controlled, can lead to the cessation of treatment, even death.

Therapies for cancer vary depending on the disease type and stage. Some patients may receive more than one therapy, combining surgery, chemotherapy, and radiation. Chemotherapy acts mainly on rapidly dividing and proliferating cells, destroying these cancerous cells and avoiding their multiplication and division. However, during this process, healthy cells are also affected (particularly those with a high proliferating index), leading to undesirable and harmful side effects [3][4]. In particular, many drugs used for cancer treatments also induce apoptosis of healthy cells in the gastrointestinal tract, provoking mucosal damage (mucositis). Compounds as commonly used as 5-fluorouracil (5-FU) and its combinations with others (FOLFOX, FOLFIRI), irinotecan, methotrexate (MTX), capecitabine, cisplatin, oxaliplatin, or doxorubicin cause mucositis among other side effects [5].

Thus, chemotherapy affects the physical and functional intestinal barrier components, including the mucus layer, the epithelium, neuroendocrine feedback signaling, and/or immune system, as well as the gut vascular barrier. This may result in an immunological response and enhanced intestinal permeability to toxic substances and may facilitate the translocation of luminal bacteria to the underlying organs or systemic circulation [6]. Importantly, gastrointestinal mucositis is associated with malnutrition and harms the general state of health of cancer patients during treatment. It provokes diverse associated symptoms in them, such as the appearance of nausea and vomiting or diarrhea, and affects nutritional intake and intestinal function [7]. Indeed, mucositis constitutes a serious problem for the application of antitumor therapies, that sometimes must be even interrupted [8][9][10]. With this in mind, many researchers have been interested in the potential of natural products and nutraceuticals to alleviate the adverse effects of antitumor drugs, especially those related to the occurrence of mucositis in the gastrointestinal tract [4][11][12]. For this, the etiopathogenic mechanisms of chemotherapy-induced mucositis need to be understood.

Pathogenesis of mucositis has been defined as a five-step model. These overlapping steps are thought to be largely driven by the activation of nuclear factor-κB (NF-κB) [13][14][15]. Indeed, NF-κB plays an important role in regulating mucositis. Briefly, NF-κB is located in the cytoplasm of cells. When inactive, the classic form of NF-κB is tightly bound to the inhibitor of nuclear factor kappa B (IκB) class of proteins, which act as an ‘inhibitor’ of NF-κB function. Following cytotoxic therapy, the bound NF-κB/IκB is phosphorylated and ubiquitinated; then, NF-κB is allowed to enter the nucleus where it is able to up-regulate many genes associated with mucositis, including pro-inflammatory cytokines, growth factors, and pro- and antiapoptotic genes [16].

In advanced stages of mucositis, chemotherapy-induced pathological effects are observed macroscopically with the formation of ulcers, but there are also microscopic changes at cellular level such as alterations in mucin secretion. Mucins are important proteins, encoded by MUC genes, that contribute to the protection of the mucosa in the gastrointestinal tract. Mucins guarantee mucosa health against the luminal contents by regulating bacterial overgrowth and penetration, as well as providing attachment sites for commensal bacteria, and the disruption of this protection leads to an increased risk of infections in patients. Damage to epithelial cells is also related to the appearance of diarrhea, typically associated with mucositis. The capacity of water absorption of the gastrointestinal tract is reduced, and the enzymes located on the brush border of the villus such as maltase, sucrase, lactase, and aminopeptidase also decrease with cell loss. Unabsorbed substances accumulate in the lumen, creating an osmotic gradient. All this makes water move into the intestinal lumen contributing to diarrhea occurrence [6][16].

Considering the key role of microbiota to maintain a healthy gastrointestinal mucosa, one of the most promising alternatives for the treatment of the adverse effects of chemotherapeutic drugs, particularly mucositis, may be the use of microbiota-related nutraceuticals, such as probiotics, synbiotics, postbiotics, or paraprobiotics [17].

Probiotics are live microorganisms and, as such, they should have certain characteristics to exert maximum therapeutic effects and minimum risks for adverse effects. Thus, they should display resistance to the gastrointestinal tract environment (low pH and bile salts), because bacteria must remain viable to colonize the intestinal tract [18]. Despite their benefits on the host’s health, it is not clear if administering live microorganisms to immunosuppressed people may produce clinical problems due to bacterial translocation (bacteremia, endocarditis,

liver abscess) [19]. These concerns would apply also to synbiotics and probiotic mixtures. In contrast, postbiotics or paraprobiotics, which are not live bacteria, would be less likely to cause harm to immunocompromised patients [20].

Probiotic properties widely differ between species, strains, or even between strain variants, which means these properties can be strain/variant specific [21]. Among the probiotics, those that have been most associated with the possibility of producing beneficial effects include the genera *Lactobacillus* and *Bifidobacterium*. These two genera include over 200 species among which many strains have been investigated as probiotics [18]. Various members of these genera are naturally associated with mucosal surfaces in the gastrointestinal tract, with mucosa protective actions [22].

Therefore, in the last years, the importance of probiotics and their derivatives is becoming more and more evident. Proof of this is the fact that in the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) guidelines for the management of mucositis (a weighted summary of the best available scientific evidence, framed in a practical clinical context), the panel suggests that probiotics containing *Lactobacillus* spp. may be beneficial for the prevention of radiotherapy- or chemotherapy-induced diarrhea in patients with pelvic malignancy [14].

2. Probiotics and Mucositis

Probiotics are being extensively studied in the context of chemotherapy-induced mucositis, especially the genera *Lactobacillus* and *Bifidobacterium*, but also *Propionibacterium* or *Saccharomyces* have aroused interest due to their properties.

2.1. Lactobacillus Strains

2.1.1. *Lacticaseibacillus casei*

Aragon et al. [23] analyzed the protective effect of milk fermented by the probiotic bacterium *Lacticaseibacillus casei* CRL 431 on a murine breast cancer model using female BALB/c mice. Mice were fed with milk fermented by *Lacticaseibacillus casei* 10 days before and 28 days after tumor injection. Probiotic administration delayed or blocked tumor development due to modulation of the immune response and reduced the area occupied by blood vessels in the tumors. This probiotic may have favorable effects against possible metastasis [23].

In a subsequent study by the same research group [24], mice bearing breast cancer were treated or not with capecitabine (500 mg/kg) and administered with the same probiotic fermented milk (PFM). PFM reduced capecitabine side effects and decreased intestinal mucositis and mortality. PFM administration also decreased diarrhea and maintained the villi length/crypt depth ratio similar to healthy animals in the small intestine. In addition, PFM by itself reduced metastasis and improved the host's immune response. Interestingly, IL-6 was significantly reduced by PFM, and the reduction of this cytokine is related to cancer survival. Capecitabine treatment decreased levels of IL-10, a cytokine with immunosuppressive and anti-angiogenic functions, and PFM maintained this profile [24].

Innovative probiotic delivery strategies, based on probiotics incorporation into protective matrices, may increase its therapeutic effect by protecting bacteria against environmental stresses. Cordeiro et al. [25] tested the protection of whey protein isolate (WPI), when added to skim milk fermented by *Lacticaseibacillus casei* BL23, and the therapeutic effect of this fermented beverage (10^9 CFU/mL) during 13 days in a murine model of mucositis induced by a single intraperitoneal injection of 5-FU (300 mg/kg). Milk supplementation with 30% (*w*/*v*) of WPI increases the survival rate of probiotic bacteria against the exposure to acid, bile salts, high temperature, and cold storage stresses. Moreover, treatment with the probiotic beverages prevented weight loss and intestinal damages in BALB/c mice receiving 5-FU. *Lacticaseibacillus casei* BL23 protective effect was further enhanced by the addition of WPI, which was able to decrease intestinal inflammation, preserve mucosal integrity, as well as prevent the degeneration of goblet cells and, consequently, improve protection and tissue repair. All these results suggest that presence of WPI maximizes the anti-inflammatory effects of this probiotic [25].

The recent study performed by Barbosa et al. [26] evaluated the effect of oral administration of *Lacticaseibacillus casei* for 18 days on the progression of 5-FU-induced intestinal mucositis (a single dose, 450 mg/kg) in female Swiss mice. *L. casei* reduced 5-FU-induced inflammation in the colon and small intestine and decreased the levels of TNF-α, IL-1β, IL-6 and malondialdehyde (a product of lipid peroxidation). In addition, a decreased expression of inducible nitric oxide (NO) synthase (iNOS) and TNF-α protein was found in the jejunum. The probiotic down-regulated NF-κB-P65 and TLR-4 gene expressions and up-regulated gene expression of the mucosal barrier proteins occludin and zonula occludens-1 (ZO-1) related with gut permeability. Furthermore, greater lactic acid bacteria population was found in the animals treated with *L. casei* compared with control groups, associated with normalization of intestinal microbiota, previously disrupted by 5-FU. Moreover, there was an increase in the mucin gene expression in the intestine of *L. casei* group. As already mentioned, the presence of mucins is important for the microbiota and protects the mucosa from bacterial overgrowth. On the other hand, *L. casei* was unable to protect against 5-FU-induced weight loss, probably due to associated anorexia and dehydration [26].

2.1.2. *Lactobacillus delbrueckii*

Lactobacillus delbrueckii subsp. lactis CIDCA 133 fermented milk has been studied in 5-FU-induced experimental mucositis in male BALB/c mice. Animals received a single intraperitoneal injection of 5-FU (300 mg/kg). The probiotic was administered over a period of 13 days, 10 days prior and 3 days post 5-FU injection and subsequent mucositis induction. The probiotic strain CIDCA 133 significantly reduced 5-FU-induced shortening of small intestine length. This finding is important because a larger area of the intestine provides enough absorption surface for nutrient uptake and reduces the loss of water and electrolytes. For that reason, treated animals were able to recover the weight loss provoked by 5-FU. Treatment with CIDCA 133 fermented milk restored the loss of architecture of the ileum mucosa, greatly reduced the 5-FU-increased intestinal permeability, prevented loss of goblet cells (due to the protection of the stem cells inside the intestinal crypts), and reduced levels of neutrophil and eosinophil infiltration. Consequently, the severity of mucositis (measured as mucosal inflammation score) was reduced. Interestingly, the administration of probiotic fermented milk was able to decrease the levels of secretory IgA (sIgA). The level of sIgA is related to the intestinal barrier and is important in the maintenance of mucosal

homeostasis and this reduction could be related to the improvement of intestinal mucosal barrier and the subsequent reduction of inflammation [27].

The same strain, under the same conditions, was investigated by Barroso et al. [28]. The probiotic provoked a decrease in the gene expression of TLR-2, TLR-4, Myd88, and NF-κB. In addition, the messenger ribonucleic acid (mRNA) expressions of proinflammatory cytokines (IL-6 and IL-1b) were downregulated while regulatory cytokine IL-10 was upregulated, further evidencing the anti-inflammatory effects that this strain can provide. Thus, CIDCA 133 could modulate inflammatory responses possibly by controlling NF-κB signaling pathway activation through upregulation of immunoregulatory molecules such as IL-10 to maintain intestinal homeostasis [28].

2.1.3. *Lacticaseibacillus rhamnosus*

There are several studies, both in animal models of mucositis and in patients undergoing chemotherapy, which have used the species *Lacticaseibacillus rhamnosus*.

The sucrose breath test (SBT) can be employed to noninvasively assess the efficacy of probiotics, determining total intestinal sucrase activity. Sucrase is an enzyme found in the brush-border membrane of mucosal cells lining the lumen of the small intestine and catalyzes the breakdown of sucrose into its constituent monosaccharides, glucose and fructose. Following ingestion of 13C-sucrose, these monosaccharides are transported to the liver and metabolized to release $^{13}CO_2$, which is exhaled from the lungs and quantified using an isotope ratio mass spectrometer. These in vivo determinations are indicative of mucosal damage, which is detected as a reduction in the parameter measured. Mauger et al. [29] used SBT to assess the efficacy of probiotics in 5-FU-induced intestinal mucositis in rats, but the probiotic was not effective to prevent it.

Despite these early negative results, other authors did find positive effects on the administration of this probiotic. Thus, Yeung et al. [30] used BALB/c mice to investigate the effects of *Lacticaseibacillus rhamnosus* supplementation in ameliorating 5-FU-induced intestinal mucositis. Animals were injected with 5-FU (30 mg/kg/day for 5 days) intraperitoneally and gavaged with a probiotic suspension of *Lacticaseibacillus rhamnosus* (1×10^7 CFU)/mL) daily. Diarrhea produced by 5-FU was attenuated following *Lacticaseibacillus rhamnosus* administration. TNF-α, IL-1β, and IL-6 mRNA expressions were up-regulated in intestinal tissues following 5-FU treatment and probiotic treatment suppressed this up-regulation, ameliorating inflammation. Histological alterations caused by 5-FU such as villus shortening, modification of crypt depth, and reduction in goblet cell numbers were restored by the probiotic [30].

Following the same protocol, Yeung et al. [31] also investigated the modulations of probiotics on gut microbiota. Stool specimens were collected for recombinant DNA (rDNA) extraction and pyrosequenced for bioinformatic analysis. At phylum and class levels of analysis, abundances of *Betaproteobacteria*, *Erysipelotrichi*, and *Gammaproteobacteria* were significantly increased by 5-FU. Probiotic supplementation did increase the abundances of *Enterobacteriales* and *Turicibacterales,* demonstrating that this strategy is capable of modulating microbiota composition [31]. The same group expanded this research using SCID/NOD mice to simulate the

immunodeficiency of chemotherapy patients. SCID/NOD animals present a functional deficit of T and B cells, macrophage deficiency, and absence of circulating complement. The probiotic *Lacticaseibacillus rhamnosus* significantly improved the diarrhea scores in 5-FU-treated animals and TNF-α, IL-1β, and IL-6 serum levels were significantly inhibited. Importantly, no evidence of bacteremia in blood cultures was found [32].

Chang et al. [33] investigated the effect of *Lacticaseibacillus rhamnosus* on FOLFOX-induced mucosal injury. FOLFOX is a combined chemotherapy treatment including 5-FU, leucovorin, and oxaliplatin commonly used for the treatment of colorectal cancer. In this study, BALB/c mice subcutaneously injected with CT26 colorectal adenocarcinoma cells were orally administered *Lacticaseibacillus rhamnosus* daily before, during, and after 5-day injection of FOLFOX regimen, for 14 days. In this way, *Lacticaseibacillus rhamnosus* dose dependently reduced the severity of diarrhea and intestinal mucositis. Histological analysis of intestinal mucosa indicated that villus shortening, lengthening of the intestinal crypts, and reduction in the villus height-to-crypt depth ratio caused by FOLFOX was alleviated dose dependently by the probiotic. *Lacticaseibacillus rhamnosus* decreased FOLFOX-induced NF-κB activity in the intestine and improved mucositis, by suppression of inflammation. Probiotic administration reduced the upregulation of proinflammatory cytokines TNF-α and IL-6 in the jejunum. In this study, the probiotic significantly reduced FOLFOX-induced apoptosis of the intestinal crypt cells by reducing the increase in the BAX/Bcl-2 ratio and favoring anti-apoptosis vias. Taxonomic analysis at the phylum level indicated that FOLFOX changed the gut microbiota composition and significantly increased the abundance of *Firmicutes* and decreased the abundance of *Bacteroidetes*. These changes were restored by *Lacticaseibacillus rhamnosus* administration suggesting that the pathogenesis of mucositis is alleviated via the gut microbiota-TLRs-NF-κB signaling pathway [33].

Interestingly, this probiotic has also been tested in patients undergoing chemotherapy [34][35]. Patients diagnosed with colorectal cancer (*n* = 150) received monthly 5-FU and leucovorin bolus injections (the Mayo regimen) or a bimonthly 5-FU bolus plus continuous infusion (the simplified de Gramont regimen) for 24 weeks as postoperative adjuvant therapy. *Lacticaseibacillus rhamnosus* GG supplementation (1–2 × 10^{10} per day) reduced grade 3 or 4 diarrhea and abdominal discomfort, and patients needed less hospital care. Furthermore, no *Lacticaseibacillus*-related toxicity was detected [34]. In children with acute leukemia receiving *Lacticaseibacillus rhanmosus* supplementation (5 × 10^9 CFU twice daily, by mouth), nausea, vomiting, and abdominal distension significantly decreased in the probiotic group [35].

2.1.4. *Lactobacillus acidophilus*

Justino et al. [36] studied the effects of *Lactobacillus acidophilus* strain, a thermophilic nonpathogenic probiotic widely used for gastrointestinal disorders. The authors developed a model of intestinal mucositis induced by 5-FU administration (a single dose of 450 mg/kg) in male Swiss mice. *L. acidophilus* (16 × 10^9 CFU/kg) was administered concomitantly with 5-FU on the first day, and for two additional days after administration. Mice with intestinal mucositis displayed significantly reduced villus height–crypt depth ratio and glutathione concentration but increased myeloperoxidase (MPO) activity and nitrite concentrations in jejunum and ileum. Furthermore, 5-FU significantly increased proinflammatory cytokines (TNF-α, IL-1β, and C-X-C Motif Chemokine Ligand 1 (CXCL-1))

concentrations, decreased IL-10 concentrations, delayed gastric emptying and gastrointestinal transit, and produced significant diarrhea. All these changes were significantly reversed by treatment with *L. acidophilus*, decreasing the inflammatory markers and functional aspects of intestinal mucositis induced by 5-FU [36].

2.1.5. *Lactiplantibacillus plantarum*

Proinflammatory cytokines and reactive oxygen species (ROS) appear to be key factors during the pathogenesis of intestinal mucositis, and agents with anti-inflammatory/antioxidant activities may serve for the treatment or prevention of this adverse effect of chemo/radiotherapy. *Lactiplantibacillus plantarum* CRL2130 is a riboflavin-overproducing strain with anti-inflammatory properties. Riboflavin is widely known to act as an antioxidant and has a potential effect against oxidative stress. Mice were intraperitoneally injected with 5-FU (50 mg/kg) once a day for 6 days and, during this period, they received this probiotic twice daily (9×10^8 CFU/mL). The administration of *L. plantarum* CRL2130 significantly attenuated the pathologic changes induced by 5-FU such as body weight loss, marked diarrhea, shortening of villus height, and the increase in the concentration of proinflammatory cytokines (IL-17, TNF-α, interferon (IFN)-γ, and IL-6 in serum and IL-17, TNF-α, IFN-γ, IL-6, IL-4, and IL-2 in intestinal contents). *Lactiplantibacillus plantarum* elevated the production of the anti-inflammatory cytokine IL-10, leading to an increase in the ratio of anti-/proinflammatory cytokines. These results indicate that the riboflavin-overproducing strain *Lactiplantibacillus plantarum* CRL2130 could be useful to prevent mucositis during cancer treatments [37].

2.1.6. *Lactobacillus johnsonii*

MTX is an anti-metabolite that exerts its cytotoxic effect through the inhibition of folate metabolism by a down-regulatory effect on the enzyme dihydrofolate reductase, resulting in the inhibition of DNA synthesis. A study aimed to evaluate commercially available yoghurt products, containing *Lactobacillus johnsonii*, in adult male Sprague Dawley rats injected with 2.5 mg/kg/day for 3 days with MTX to induce intestinal mucositis. Although the cow's yoghurt containing *L. johnsonii* (10^7 organisms/L) was effective in reducing intestinal damage provoked by MTX, it was not as effective in restoring functionality as evidenced by brush-border enzyme activity, an indicator of damage in the small intestinal epithelium [38].

2.1.7. *Lacticaseibacillus reuteri*

Yeung et al. [31] investigated the potential changes of 5-FU treatment and the modulations of probiotics on gut microbiota in male BALB/c mice. Animals were fed with 100 µL of a suspension containing 1×10^7 CFU *Lacticaseibacillus reuteri* DSM 17938 daily and were administered with 5-FU (30 mg/kg/day) for 5 days. In the fecal microbial community, probiotics supplementation increased the abundances of *Enterobacteriales* and *Turicibacterales*. The authors concluded that the modulation of microbiota by administration of probiotics may be a useful strategy for the treatment of gastrointestinal side effects of chemotherapy [31].

2.1.8. *Limosilactobacillus fermentum*

Not all *Lactobacillus*-based probiotics have been found to be effective in the treatment of mucositis. In the study performed by Mauger et al. [29] in Dark Agouti rats, this probiotic was administrated by gavage for 10 days (10^6 CFU/mL) and intestinal mucositis was induced on day 7 by intraperitoneal injection of 5-FU (150 mg/kg). At the doses tested, *Limosilactobacillus fermentum* could not prevent the small intestine damage caused by 5-FU. Possible explanations for the lack of efficacy may be related to the dosage, timing, and duration of delivery, or lack of suitability of the strain used for the mucositis setting.

2.2. Bifidobacterium Strains

2.2.1. *Bifidobacterium bifidum*

The study performed by Kato et al. [39] examined the effect of *Bifidobacterium bifidum* G9-1 (BBG9-1) on intestinal mucositis, especially in relation to its effects on apoptosis, inflammatory cytokine expression, and dysbiosis. In this investigation, mice received repeated administration of 5-FU (50 mg/kg) for 6 days. BBG9-1 (10^7–10^9 CFU) was administered orally once daily for 9 days, beginning 3 days before the onset of 5-FU treatment. Probiotic administration significantly attenuated body weight loss and reduced the severity of diarrhea induced by 5-FU. Furthermore, BBG9-1 abrogated the macroscopic and histological changes associated with 5-FU: reduction in small intestine length, shortening of the villi, and destruction of the crypts. Additionally, BBG9-1 significantly attenuated 5-FU-induced increase in MPO activity and TNF-α and IL-1β expression. Curiously, BBG9-1 failed to prevent the initial induction of apoptosis despite suppression of the secondary inflammatory responses. Interestingly, authors found that the clustering of the intestinal microbiota structure was altered by 5-FU, with a decrease in the abundances of *Firmicutes* and *Actinobacteria,* mostly comprised of Gram-positive bacteria, and increasing the abundances of *Bacteroidetes* and *Proteobacteria*, mostly Gram-negative bacteria. Treatment with BBG9-1 partially restored the normal composition of microbiota [39].

2.2.2. *Bifidobacterium breve* Strain Yakult

In pediatric patients undergoing chemotherapy treatments against leukemia, the enteral administration of the probiotic *Bifidobacterium breve* strain Yakult was evaluated as a method to prevent infections. In immunocompromised patients, one of the main causes of infection is the alteration of endogenous intestinal flora and its colonization by pathogenic bacteria followed by translocation through the gut mucosa and systemic dissemination. For this study, a placebo-controlled trial was performed, and 42 patients received probiotic or placebo. The probiotic product contained 10^9 freeze-dried, living *B. breve* strain Yakult. The frequency and duration of febrile episodes was lower in the probiotic group but there was no significant difference in the frequency and duration of diarrhea. Fecal bacteriological examination demonstrated the disruption of the intestinal microbiota after chemotherapy, with an increase in the population levels of *Enterobacteriaceae* more pronounced in the placebo group. Administration of *B. breve* strain Yakult resulted in a significantly higher count of *Clostridium leptum* subgroup after 2 weeks, indicating that the initiation of probiotic administration enhanced the intestinal occupation by anaerobes. Facultative anaerobes such as *Enterococcus* decreased only in the probiotic group. These results demonstrate its effect on maintenance of favorable intestinal microflora and suggest that administration of *B. breve*

strain Yakult could be an effective approach for achieving clinical benefits in immunocompromised hosts by improving their intestinal environments [40].

2.2.3. *Bifidobacterium infantis*

The benefits on mucositis of the probiotic *Bifidobacterium infantis* have been studied [41][42]. *B. infantis* is a commensal microbe isolated from the human gastrointestinal mucosa and has shown beneficial effects on gastrointestinal disease by modulating the immune function [42].

Male Sprague–Dawley rats were treated with a single intraperitoneal injection of 5-FU (150 mg/kg) and *B. infantis* (1×10^9 CFU) was administered for 11 days, starting from 7 days before 5-FU injection. *B. infantis* improved body weight and reduced 5-FU-induced diarrhea. Animals treated with the probiotic restored villus height in jejunum, displayed increased expression of proliferating cell nuclear antigen (PCNA), reduced expression of NF-κB, and decreased cell damage. Pro-inflammatory factors and MPO concentration were decreased compared with the 5-FU group. These data suggest that the probiotic *B. infantis* is effective in reducing chemotherapy-induced intestinal mucositis and the occurrence of diarrhea in rats [41].

This probiotic has also proven to be useful in palliating mucositis caused by a combination of chemotherapeutic agents, 5-FU and oxaliplatin, due to its role in the regulation of T cell in a model of colorectal cancer in rats. In this model, animals were injected dimethyl hydrazine (DMH) subcutaneously for 10 weeks, and then injected with SW480 cells in the rectal mucosa. Chemotherapy was applied in these rats and a group of animals was treated with the probiotic [42]. The probiotic improved weight loss and restored intestinal villus height and crypt depth compared with the chemotherapy group. Interestingly, the authors demonstrated that this probiotic was able to modulate the activity of immune cells. During mucositis, effector T-helper cells (Th1, Th2 and Th17) released pro-inflammatory cytokines and initiated excessive inflammation, resulting in intestinal mucosal damage. This study showed that the levels of Th1 cells and derived cytokines (IL-2, IL-12, and IFN-γ) were up-regulated in the chemotherapy-induced intestinal mucositis rats and these effects could be reversed by *B. infantis* administration. *B. infantis* also down-regulated the level of T-bet (a Th transcription factor) that appears to regulate lineage commitment in CD4-Th lymphocytes, in part, by activating IFN-γ. In addition, the results showed a decrease in mRNA for the lineage-specific transcription factor RORγt in chemotherapy-induced intestinal mucositis in rats fed with *B. infantis*. The orphan nuclear receptor RORγt, is the pivotal transcription factor to Th17 differentiation. These results suggest that *B. infantis* suppressed Th17 responses by regulating its cytokines and differentiation-related factors. In this study, *B. infantis* promoted $Foxp3^+$ Treg (regulatory T cells) responses in association with increased levels of IL-10 and transforming growth factor (TGF)-β in rats with intestinal mucositis. $Foxp3^+$ Tregs are essential for normal immune homeostasis by suppressing T-helper effector cells. Overall, the data from this study seem to indicate that *B. infantis* can attenuate chemotherapy-induced intestinal mucositis via suppressing Th1 and Th17 responses as well as promoting $Foxp3^+$ Treg responses in rats with colorectal cancer [42].

2.2.4. *Bifidobacterium lactis*

SBT was employed to noninvasively assess the efficacy of probiotics in 5-FU-induced intestinal mucositis in an animal model using Dark Agouti rats. *Bifidobacterium lactis* BB12 was administered by oral gavage for 10 days and mucositis was induced on day 7 by intraperitoneal injection of 5-FU (150 mg/kg). Rats were sacrificed 72 h after 5-FU injection or vehicle (saline). In these experimental conditions, the probiotic offered no protection for mucositis at the dose tested [29].

2.3. Streptococcus thermophilus

Some studies have shown that the administration of *Streptococcus thermophilus* can reduce intestinal mucositis in animal models induced by chemotherapy agents such as 5-FU and MTX. This probiotic has been useful to prevent weight loss, attenuate diarrhea, and decrease intestinal damage. *S. thermophilus* is a Gram-positive, lactic acid producer, and ovoid-shaped bacterium appearing in pairs or in short chains. The capacity of production of SCFAs (acetate, propionate, and butyrate) may have positive effects for treatment of mucositis [43].

The study of Whitford et al. [44] analyzed the therapeutic potential of live *S. thermophilus* TH-4 (TH-4), dead TH-4, and TH-4 supernatant in rats treated with a single dose of 5-FU (150 mg/kg). Treatments were administered daily from two days before to three days after the administration of 5-FU, via orogastric gavage. Although in these conditions the probiotic was unable to ameliorate 5-FU-induced mucositis, live TH-4 may still have therapeutic potential in cancer patients, due to its capacity to decrease mitotic activity and reduce crypt fission and its potential to combat neoplasia [44].

Tooley's research group [45] investigated the effects of orally ingested TH-4 on chemotherapy-induced small intestinal damage in female Dark Agouti rats using the noninvasive SBT test. Gastrointestinal damage was induced with MTX (1.5 mg/kg). Daily treatment with TH-4 at doses of 10^9 (high), 10^8 (low) CFU/mL, was performed 48 h pre- and 96 h post-MTX injection. Importantly, the administration of TH-4 at these two different doses produced differing results; when used at low doses, TH-4 offered no protection, whereas administration of TH-4 at the higher dose partially prevented the loss of body weight and the decrease in food intake and was capable of partially attenuating mucositis and normalizing SBT results. Again, these results highlight the importance of dosage in probiotic administration protocols to treat the side effects of chemotherapy [45].

To further investigate the therapeutic potential of this probiotic, the same research group carried out a study to analyze the effects of TH-4 on small intestinal damage and tumor progression in tumor-bearing rats [46]. Female tumor-bearing Dark Agouti rats (mammary adenocarcinoma) developed small intestinal damage induced via the administration of MTX (1.5 mg/kg) at 0 and 24 h. Animals were daily administrated with the high dose of TH-4 (10^9 CFU/mL) −48 to +96 h post-MTX. When TH-4 was administered to MTX-treated rats with mammary adenocarcinoma, it yielded no protection. There could be several possible explanations for these findings. For example, the degree of intestinal damage was more severe in the tumor-bearing animals, compared with the damage observed in the non-tumor bearing model of mucositis [45]. Considering this probiotic was capable of increasing folate levels in reconstituted milk, the mechanism of protection by TH-4 in non-tumor bearing animals

may have been the result of delivering a micro dose of folate to the site of damage. Nevertheless, the dose of 10^9 CFU/mL was insufficient to diminish the severity of mucositis in the tumor presence [46].

The effects of this probiotic have also been studied with the antitumor drug doxorubicin (20 mg/kg) [47] in female Dark Agouti rats, gavaged with TH-4 (10^9 CFU/mL) for 9 days. In this context, TH-4 partially prevented the loss of body weight associated with early induced mucositis development (24 h post-doxorubicin administration). This minimal amelioration may be due to folate production as a likely mechanism of TH-4 action against MTX-induced mucositis. Interestingly, in the saline-treated animals receiving TH-4, an increase in polymorphonucleocytes and lymphocytes in jejunum and ileum was observed. This could be indicative of an immunostimulatory response initiated through TH-4 administration alone. However, this effect was not observed in doxorubicin-treated rats receiving TH-4, most likely due to a masking effect provoked by the chemotherapeutic agent. Accordingly, it should be taken into consideration the potential for certain probiotics to impact on immune defenses. In general, the use of probiotics should be taken with caution, as adverse effects may occur and should be carefully analyzed. Further studies into TH-4 are required to confirm its applicability to chemotherapy regimens [47].

Levit et al. [48] evaluated two folate-producing strains, *S. thermophilus* CRL 808 and *S. thermophilus* CRL 415, against 5-FU-induced mucositis in mice. Mice were daily injected with 5-FU (50 mg/kg) to induce intestinal mucositis, and orally administered with folate-producing strains (100 ng/mL) during six days. *S. thermophilus* CRL 415 did not improve any of the parameters evaluated but *S. thermophilus* CRL 808 had the potential to prevent intestinal mucositis induced by 5-FU, decreasing diarrhea scores, improving histological alterations, and reducing jejunal inflammation. This effect was accompanied by decreased pro-inflammatory IL-6 and increased anti-inflammatory IL-10 in serum. The lack of a beneficial effect of *S. thermophilus* CRL 415 may be because this strain contains lower intracellular folate concentrations compared with *S. thermophilus* CRL 808. Therefore, the administration of selected folate-producing bacteria could be useful to attenuate the symptoms of intestinal mucositis in patients undergoing chemotherapy [48].

Shen et al. [43] studied if *S. thermophilus* ST4 separated from raw milk displays protective activity against intestinal mucositis induced by 5-FU (50 mg/kg/day). BALB/c mice received 100 µL of the probiotic suspension containing 5×10^8 CFU, daily for 17 days. 5-FU intraperitoneal injection was administered after the 10th day, for three consecutive days. Administration of *S. thermophilus* alleviated diarrhea, decreased the infiltration of macrophage into distal mucosa and protected the structural integrity of small intestine and colon tissue. In addition, *S. thermophilus* ST4 significantly increased fecal acetic acid concentration, one of the common and functional SCFAs. SCFAs produced from bacterial fermentation may provide energy for epithelial cells essential for the development and mediation of the intestinal barrier function. Proinflammatory cytokines TNF-α, IL-1β, and IL-6 were significantly increased following 5-FU treatment, and this effect was attenuated by *S. thermophilus*. In addition, TNF-α is a key factor in the caveolin-1-mediated internalization of occludin and, therefore, its reduction improved gut permeability [43].

2.4. Propionibacterium freudenreichii

Propionibacterium freudenreichii is an important species of dairy propionibacteria that plays an important role in food transformation, particularly in cheese ripening. It is a Gram-positive, non-motile, non-spore forming, and anaerobic to aerotolerant beneficial bacterium that is generally recognized as safe (GRAS). Dairy propionibacteria have a great probiotic potential, as they produce important metabolites such as the SCFAs acetate and propionate, vitamins B9 and B12, as well as 1,4-dihydroxy-2-naphthoic acid (DHNA) and 2-amino-3-carboxy-1,4-naphthoquinone (ACNQ) [25].

Only a few studies have tested the immumodulatory properties of this probiotic. *P. freudenreichii* CIRM-BIA 129 strain possesses extractable surface proteins, including surface-layer protein (Slp) B, involved in anti-inflammatory effect and in adhesion to epithelial cells. The work by Do Carmo et al. [49] studied the importance of SlpB in *P. freudenreichii* ability to reduce mucositis inflammation both in vitro and in vivo, comparing *P. freudenreichii* wild type with a mutated strain of *P. freudenreichii* ΔslpB, lacking the SlpB protein. First, in an in vitro assay, *P. freudenreichii* WT reduced the expression of proinflammatory cytokines IL-8 and TNF-α in lipopolysaccharide (LPS)-stimulated HT-29 cells, but *P. freudenreichii* ΔslpB, lacking the SlpB protein, failed to do so. Hereafter, both strains were investigated using an in vivo model in BALB/c mice, after induction of mucositis by a single intraperitoneal injection of 5-FU (300 mg/ kg). The probiotics were administered daily for 10 days before 5-FU injection. Wild-type strain prevented weight loss, reduced inflammation and consequently histopathological scores. The claudin-1 expression, decreased in mucositis, was restored by consumption of the probiotic, but not by the mutant, in accordance with its inability to restore gut permeability. Moreover, the wild type of the probiotic produced a decrease in sIgA levels that could be correlated with the improved integrity of the epithelial barrier and consequent protection against pathogens. Altogether, the findings of this work demonstrated, by in vitro and in vivo approaches, that the mutation of the extractable surface protein slpB gene directly affects the probiotic effects of *P. freudenreichii* [49].

P. freudenreichii CIRM-BIA138 (*P. freudenreichii* 138) has been tested in combination with a protective whey matrix (WPI) to reduce the effects of bacteria exposure to stressful environments and increase their probiotic properties. Although a probiotic beverage fermented by *P. freudenreichii* 138 was able to decrease 5-FU-induced intestinal inflammation in BALB/c mice, with preservation of the mucosal integrity and reduced weight loss, the presence of WPI did not improve these effects. In contrast, as mentioned above, *L. casei* BL23 protective effect was further enhanced by the addition of WPI. These results suggest that whey protein enhancement of probiotic is strain dependent [25].

2.5. Clostridium butyricum

Clostridium butyricum is a butyrate-producing human gut symbiont. *C. butyricum* consume undigested dietary fibers and generate SCFAs, specifically butyrate and acetate. In addition, *C. butyricum* may modulate the composition of the gut microbiome, possibly increasing certain beneficial bacterial taxa such as *Lacticaseibacillus* and *Bifidobacterium* [50].

The role of *C. butirycum* in patients undergoing chemotherapy was investigated in the study performed by Tian et al. [51]. A total of 41 participants with lung cancer subjected to platinum-based chemotherapy were administered with *C. butyricum* or placebo for 3 weeks. The incidence of chemotherapy-induced diarrhea was lower in the group treated with the probiotic and the systemic inflammatory response system was reduced. *Firmicutes* in the placebo group decreased significantly; however, in the *C. butyricum* group, the variation was minor. The genera producing SCFA tended to increase and the pathogenic genera tended to decrease in the *C. butyricum* group and a notable increase in beneficial flora was detected, including *Clostridium* and *Lacticaseibacillus*. The present study highlighted that *C. butyricum* reduced chemotherapy-induced diarrhea in patients with lung cancer, helping to maintain the condition of the intestinal flora [51].

2.6. Saccharomyces Strains

Saccharomyces cerevisiae is a brewer's, baker's yeast with probiotic properties. Several taxonomic studies on *S. boulardii* have indicated that it should be considered as a strain of *Saccharomyces cerevisiae* and, as such, it should be referred to as *Saccharomyces cerevisiae var. boulardii* [52]. However, other studies suggest that they are different enough to be considered separate species. Despite the striking relatedness in molecular phylogeny and typing, *S. boulardii* does possess identifiable distinct traits and is physiologically and metabolically distinct from *S. cerevisiae*. *S. boulardii* is incapable of producing ascospores, switching to haploid form, or using galactose as carbon source. It is more resistant to temperature and acidic stresses, but less resistant to bile salts [22]. Whatever the case may be, until now, *Saccharomyces boulardii* has been the only yeast commercialized worldwide as a probiotic for humans [53].

2.6.1. *Saccharomyces cerevisiae*

To evaluate the potential probiotic effects of *Saccharomyces cerevisiae* UFMG A-905 (Sc-905), Bastos et al. [54] investigated its effects in a mucositis model induced by irinotecan (75 mg/kg) in Swiss male mice. For this, they tested different administration possibilities: pre- or post-treatment with viable or inactivated yeast for 5 days. Their study included the effects of Sc-905 cells killed by heat, due to the possibility of some risk for immunocompromised patients when using live probiotics. In this study, only post-treatment with viable Sc-905 (0.1 mL of 10^9 CFU/mL) was able to protect mice against the damage caused by chemotherapy. Histological analysis of the jejunum showed the improvement of the architecture of intestinal mucosa, reduction of the mucosal inflammation, and prevention of loss of goblet cells in animals treated with irinotecan; furthermore, this treatment was able to reduce the alteration of intestinal permeability. Sc-905 yeast reduced the damage caused by the formation of ROS during chemotherapy, such as lipid peroxidation, and was shown to provide greater availability of glutathione (GSH), which quenches ROS [54].

There is an increased interest in yeasts enriched with selenium as a dietary supplement, which may protect against oxidative stress due to their ability to incorporate inorganic selenium and convert it into selenomethionine [55]. Oral administration of Sc-905 enriched with selenium was evaluated as an alternative to alleviate the side effects of 5-FU-induced mucositis in Swiss mice. The researchers administrated a single intraperitoneal injection of 5-FU (300 mg/kg) and a daily dose of 10^8 CFU of Sc-905 enriched (or not) with selenium for 10 days. Both probiotics

demonstrated positive effects, but selenium-enriched yeast proved to be more effective to reduce MPO activity, levels of the neutrophil chemoattractant cytokine CXCL1/KC, histopathological tissue damage, oxidative stress (lipid peroxidation and nitrite production), and the increase in NO levels associated with the induction of mucositis. However, only selenium-enriched yeast reduced eosinophil peroxidase activity produced by 5-FU in the small intestine Altogether, this study clearly showed that the oral administration of Sc-905 protected mice against mucositis induced by 5-FU, and that this effect was potentiated when the yeast was enriched with selenium [55].

2.6.2. *Saccharomyces boulardii*

The thermophilic non-pathogenic yeast *Saccharomyces boulardii* has been investigated on irinotecan-induced mucositis and diarrhea in male Sprague–Dawley rats. Irinotecan (60 mg/kg) was administered intravenously for four consecutive days and *Saccharomyces boulardii* (800 mg/kg) was administered for 3 days before administration of irinotecan and 7 days throughout the experiment. In the jejunum, leukocyte infiltration and inflammation were significantly lower in rats which received the probiotic. This yeast prevents intraluminal solute accumulation and the subsequent osmotic diarrhea by increasing the enzymes in the brush border in chemotherapy-exposed animals. Moreover, *S. boulardii* contains significant amounts of polyamines (spermidine and spermine). In the small intestine, these polyamides are absorbed by semi-active transport system; via polyamines, *S. boulardii* has effects on cell growth, differentiation, maturation, and apoptosis, controlling mitogen-activated protein (MAP) kinase (MAPK) and NF-κB. The synthesis of the proinflammatory cytokines TNF-γ and IL-8 are controlled by MAPK and NF-κB. In this way, *S. boulardii* modifies the signaling pathways implicated in the synthesis of proinflammatory cytokines and contributes to reducing irinotecan-induced mucosal damage [56].

Justino and collaborators have conducted several studies on the efficacy of this probiotic in relieving mucositis caused by a single intraperitoneal administration of 5-FU (450 mg/kg) in a murine model [57][58]. Animals were treated with *S. boulardii* (16×10^9 CFU/kg) for 3 days. *S. boulardii* reversed 5-FU-induced changes in gastrointestinal function, enhancing intestinal transit and gastric emptying and attenuating diarrhea and weight loss. In parallel, this probiotic induced the recovery of intestinal permeability measured by lactulose: mannitol ratio. In jejunum and ileum, *S. boulardii* significantly reversed the histopathological changes in intestinal mucositis and reduced the inflammatory parameters such as neutrophil infiltration, MPO activity, nitrite concentration, proinflammatory cytokines TNF-α and IL-1β, and also reduced GSH concentration. In addition, treatment with *S. boulardii* significantly decreased apoptosis in intestinal crypt cells in the jejunum and ileum. Furthermore, it modified the Toll-like/MyD88/NF-κB/MAPK pathway in an infection model of Caco2 cells exposed to LPS and treated with 5-FU [58]. Similar results were observed in 5-FU-mediated experimental intestinal mucositis in mice. The pharmacological modulation of this pathway by *S. boulardii* might have a relevant therapeutic impact [57].

Despite promising results on the use of this yeast to alleviate the mucositis produced by chemotherapy, some results have been contradictory. In the study performed by Maioli et al. [59], pretreatment for 10 days with *S. boulardii* (10^9 CFU/mL) was not able to prevent the effects of experimental mucositis induced by 5-FU (300 mg/kg) such as the increase in intestinal permeability or alterations in the tissue architecture [59].

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