Effects of different probiotic strains B. lactis, L. rhamnosus and L. reuteri on brain-intestinal axis immunomodulation in an endotoxin-induced inflammation

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Abstract
The study evaluated the effects of supplementation with three different probiotic strains Bifidobacterium lactis (LACT GB™), Lactobacillus rhamnosus (RHAM GB™) and Lactobacillus reuteri (REUT GB™) on brain-intestinal immunomodulation in an animal model of LPS-induced inflammation. Fifty mice Balb/C were distributed into five groups: control; lipopolysaccharide (LPS); LPS + B. lactis (LACT GB™); LPS + L. rhamnosus (RHAM GB™); and LPS + L. reuteri (REUT GB™). The animals were supplemented with their respective probiotic microorganisms daily, for 30 days, at a concentration of 1 × 10⁹ CFU/animal/day. After 30 days of supplementation, animals received the inflammatory insult by LPS (15 mg/kg). Behavioral tests, oxidative stress and inflammation were performed, as well as gut and brain histology. In the behavioral test, LPS + B. lactis group was less anxious than the other groups. Serum interleukin IL-1β and IL-6 levels increased in all groups that received the LPS insult, and there was a reduction in inflammation in the supplemented groups when compared to the LPS group in brain and gut. There is a reduction in myeloperoxidase activity and oxidative stress in groups supplemented with probiotics. In intestine histological analysis occurs damage to the tissue integrity in the LPS group, in the other hand, occurs preservation of integrity in the probiotic supplemented animals. In the brain, infiltrates of perivascular inflammatory cells can be seen in the LPS group. The three probiotic studies showed efficient immunomodulating activity and ensured integrity of the intestinal barrier function, even after the severe insult by LPS. These results show the important role of probiotics in the gut–brain axis.

Keywords Probiotics · Gut–brain axis · Inflammation · Immunomodulation

Introduction
The supplementation of probiotics has attracted the population’s interest in health promotion and disease prevention. Probiotics are live microorganisms that provide health benefits to the host [1]. The main advantages of probiotic ingestion reported in systematic reviews are related to several different conditions. Those include prevention and treatment of necrotizing enterocolitis [2]; decreased incidence of diarrhea associated with antibiotic use [3]; decreased duration of infectious and inflammatory diseases [4]; regulation of intestinal transit [5]; relief of irritable bowel syndrome symptoms [6]; decrease in the incidence of upper respiratory tract diseases [7]; reduction in allergy symptoms, serum cholesterol concentration, stimulation and modulation of the immune system and modulation of gene expression [8].

Probiotics have been widely studied and characterized as modulators of humoral, cellular, and non-specific immunity [9, 10], such as decreased proinflammatory cytokines [11]. In addition, several studies have reported that probiotics also produce antioxidants and reduce lipid peroxidation [9–12].

On the other hand, the gut microbiota has the function of producing metabolites that can have positive effects on the
host, including anti-inflammatory and antioxidant activity, regulating the intestinal barrier function, in addition to participating in the development and maintenance of the immune and sensory functions of the gut [13]. The literature reports a series of evidence that the intestinal microbiota communicate with the central nervous system (CNS) through the gut–brain axis, possibly through neural, endocrine and immune pathways [14], where interactions in gut–brain axis are associated with intestinal inflammation, chronic abdominal pain syndromes and eating disorders [15], and their modulation is associated with stress response and behavior [16].

The genus *Lactobacillus* includes various Gram-positive facultative anaerobic or microaerophilic rod-shaped bacteria, which are able to produce lactic acid through glucose metabolism. Particularly, *Lactobacillus rhamnosus* improves immune status, particularly in viral infections [17] and has even been effective in reducing viral-associated pulmonary damage through controlling immune-coagulative responses and clearing respiratory viruses [18]. On the other hand, *Lactobacillus reuteri* strain has antimicrobial and immunomodulating properties, since it produces metabolic such as reuterin (Mu et al., 2018), acetic acid, ethanol and lactic acid [19, 20].

The genus *Bifidobacterium* includes various Gram-positive non-motile anaerobic bacteria. They are endosymbiotic inhabitants of the gastrointestinal tract of mammals, including humans [21]. Strains of the genus *Bifidobacterium* are also known for their variety of resistance mechanisms to bile salts. *Bifidobacterium* species together with other probiotics have been proven to treat constipation [22], antibiotic-associated diarrhoea [23], maintaining remission of disease activity of gut inflammation and moderate ulcerative colitis [24, 25], prevention as well as treatment of necrotizing enterocolitis in newborns [26], reducing the development of disease risk for eczema, food allergies [27], among others. A review of the literature has shown the effects de *Bifidobacterium lactis* in treatment of functional constipation in adults [22]; reduction of incidence of urinary tract infections in children [28]; modulation of brain activity [29]; reduction of necrotizing enterocolitis in preterm infants [30]; reduction of risk of upper respiratory illness [31].

Thus, the present study evaluated the effects of supplementation of three different probiotic microorganisms *Bifidobacterium lactis* (LACT GB™), *Lactobacillus rhamnosus* (RHAM GB™) and *Lactobacillus reuteri* (REUT GB™) on intestinal health, anti-inflammatory activity, antioxidant and anxiety in an animal model of LPS-induced inflammation.

### Materials and Methods

#### Animals

The experimental procedures involving animals were performed in accordance with the Brazilian law of animal welfare and with the approval of our institutional ethics committee (protocol number: 22/2021. Adult male mice (Balb/C), 60 days old, weighing between 20 and 30 g were used. The mice were kept in light–dark cycles of ±12 h (7:00 am to 7:00 pm) at a temperature between 18 and 22° C, relative humidity between 55 and 65%. The animals had free access to water and food.

#### Probiotic strains

The probiotic microorganisms used in this study were supplied by the company Gabbia Biotechnology: *Bifidobacterium lactis* (LACT GB™), *Lactobacillus rhamnosus* (RHAM GB™) and *Lactobacillus reuteri* (REUT GB™).

#### Experimental design

The animals were divided into five groups, each group consisting of 10 animals:

1. Group control
2. Group LPS
3. Group LPS + *Bifidobacterium lactis* (LACT GB™).
4. Group LPS + *Lactobacillus rhamnosus* (RHAM GB™).
5. Group LPS + *Lactobacillus reuteri* (REUT GB™).

After the acclimation period (seven days), treatment started. Treated groups were supplemented, via gavage, once a day with their respective probiotics for 30 days, at a concentration of 1 × 10⁹ CFU/animal/day.

After 30 days of supplementation, the animals received an inflammatory insult by intraperitoneal LPS at a dose of 15 mg/kg. On the 32nd day, a behavioral test was performed, and then animals were euthanized by decapitation (guillotine) to collect serum, whole brain and intestine samples for subsequent analyses.

#### Behavior test—Elevated plus maze

The elevated plus-maze test was performed to assess anxiety-like behavior [32]. The equipment consists of two open arms (50 × 10 cm) and two closed arms (50 × 10 × 40 cm) arranged perpendicularly forming a central platform (5 × 5 cm). The experiments were conducted in a dark room with a red light positioned 50 cm high from the central platform. The animals were placed on the central platform and had 5 min to explore the device. The parameters evaluated were: length of stay in the closed and open arms and the total number of entries into both.
Cytokines levels

The concentrations of IL-1β, IL-6 and IL-10 were determined in serum, brain, and intestine using the enzyme immunoassay technique (ELISA) in a microplate reader using a commercial kit (R&D System—USA). Results were expressed as pg/ml.

Myeloperoxidase Activity

Myeloperoxidase activity is indicative of tissue neutrophil infiltration. Tissue was homogenized (50 mg/ml) in 0.5% hexadecyltrimethylammonium bromide and centrifuged. The suspension was sonicated, and an aliquot of the supernatant was mixed with 1.6 mM TMB and 1 mM H₂O₂ solution. MPO activity was measured spectrophotometrically at 650 nm at 37 °C. Results were expressed as mU/mg protein [33].

Nitrite/nitrate

The nitrite/nitrate concentration is indicative of the amount of nitric oxide (NO) present in the samples. Concentration was measured by the Griess reaction, reading at absorbance of 550 nm using a microplate reader. Results were expressed as nmol/mg protein [34].

Lipid Oxidative Damage (TBARS)

TBARS is a technique that assesses lipid damage through the reaction to thiobarbituric acid. Briefly, the samples were mixed with 1 ml of 10% trichloroacetic acid for deproteinization and then incubated with 1 ml of 0.67% TBA. Afterward, samples were heated in a boiling water bath for 30 min. Equivalents to malondialdehyde (MDA) were determined by absorbance at 532 nm, using 1,1,3,3-tetramethoxypropane as external standard. Results were expressed as MDA equivalents (nmol/mg protein) [35].

Histology for evaluation of gut inflammation

Immediately after death, samples of the brain and terminal ileum were removed. The samples were washed with saline solution and immediately immersed in 4% paraformaldehyde and remained for 48 h; after this period, the tissues were removed, placed in different concentrations of 70%, 80% and 90% ethanol and embedded in paraffin. Longitudinal Sects. (5 μm) of colon and brain tissue were cut and stained with hematoxylin and eosin (HE). Digital micrographs were taken with an inverted Nikon microscope. Inflammatory alterations in the tissue were evaluated independently by a researcher and a pathologist blinded to information on treatment. Semiquantitative scoring was performed according to Erben et al. (2014) [36].

Statistical analysis

Variables are presented as mean ± standard deviation and compared using one-way analysis of variance (ANOVA) followed by Tukey’s test when F is significant. All tests were performed using SPSS version 21 and/or GraphPad Prism 7.0. In all analyses, a p-value <0.05 was adopted as a level for statistical significance.

RESULTS

Elevated plus-maze test was performed in order to assess anxiety-like behavior in animals. As expected, LPS induced an anxiety-like behavior (Fig. 1). The animals supplemented with Bifidobacterium lactis (LACT GB™)
had more entries in the open arms when compared to the LPS group (Fig. 1).

In order to assess the profile of inflammation and the potential immunomodulation of probiotic microorganisms, the quantification of cytokines in serum, brain and gut was performed. The results are shown in Fig. 2. In serum, interleukin IL-1β and IL-6 levels increased in the LPS group and were not affected by any probiotic. There were no statistically significant differences in serum IL-10 levels. In the brain the levels of interleukin IL-1β were lower in the groups supplemented with *Lactobacillus reuteri* (REUT GB™) and *Bifidobacterium lactis* (LACT GB™), after an inflammatory insult. IL-6 interleukin levels were reduced in all supplemented groups. In the gut, the levels of interleukin IL-1β and IL-6 were reduced in all groups supplemented after inflammation. In the LPS group there is a reduction in IL-10 levels, and the *Lactobacillus reuteri* (REUT GB™) group IL-10 levels were similar to the control group.

As a more general marker of tissue inflammation, myeloperoxidase activity was measured in gut and brain (Fig. 3). There was a statistically significant reduction in myeloperoxidase activity in the groups supplemented with probiotics only in the brain.

Oxidative stress was also measured in gut and brain using nitrite/nitrate concentration and TBARS technique. In both, there was a statistically significant reduction in nitrite/nitrate concentration in all supplemented groups. In the gut, there was a statistically significant reduction in lipid peroxidation in all supplemented groups. In the brain, this reduction was verified only in the group supplemented with *Lactobacillus reuteri* (REUT GB™) (Fig. 4).

A heat-map has been constructed to clarify the results on the immunomodulatory effects of the three strains studied on gut–brain axis. The heat-map provides an immediate visual summary of our results and shows important and significant changes between strains in relation to cytokine production summarizing the graphs presented in Figs. 2, 3 and 4.

![Fig. 2](image-url) Cytokines levels IL-1, IL-6 and IL-10 in serum (A, B, C), brain (D, E, F) and gut (G, H, I) in mice supplemented with probiotics that received an inflammatory insult by LPS. Mean ± SD. ANOVA test. * difference of control group; # difference of LPS group. n=6–8. p < 0.05
Histological analysis of the gut and brain were performed (Fig. 5). Semiquantitative scoring was performed in the gut. The effect of LPS on tissue integrity was verified as well as inflammatory infiltrate. In supplemented animals, the villi remain intact, as well as the absence of inflammatory infiltrate. In addition, the Bifidobacterium lactis (LACT GB™) group had a higher number of goblet cells per villi, indicating greater efficiency in mucus production ($p < 0.005$).

In the brain tissue, there is an increase in the number of perivascular inflammatory cell infiltrates in the LPS group (only qualitative analysis). This condition was not verified in the groups supplemented with probiotic microorganisms. Finally, a graphical abstract has been summarizing our findings. Different probiotic strains can influence the immunomodulatory response releasing different pro- and anti-inflammatory cytokines, with a role in the balance of dysbiosis.

Discussion

Our study shows the bidirectional relationship between the intestine–brain axis and the role of different probiotic strains in the presence of inflammatory insult, improving anxiety-like behavior, reducing inflammation, oxidative stress and tissue damage.

Bidirectional communication between brain and gut has long been recognized. There is a growing body of evidence...
documenting the ability of prebiotics, probiotics, synbiotics and other diets to normalize dysbiosis associated with psychological disorders [37, 38]. Numerous works focus on the impact of the microbiota on behaviors such as anxiety or depression [39–41]. Anxiety and depressive episodes are associated with dysregulation of the HPA axis [42]. Evidence from experiments carried out in animals with altered intestinal microbiota, whether GF mice or conventionally animals treated with antibiotics and/or probiotics or infected, all indicate that rodent behavioral responses are impacted when the bacterial status of the gut is manipulated [43–45].

Probiotics can improve host immunity modulating and properly maturing the immune system [46]. Our results indicate immunomodulatory activity by probiotics, since they were able to reduce the inflammatory response through the reduction of different proinflammatory players (see Graphical abstract). LPS produced by Gram-negative bacteria enters in the circulation through intestinal permeability, activating the immune response and TLR4/NF-kB signaling pathway [47].

This result contributes to the gut–brain axis relationship. Some studies suggest that an improvement in the symptoms associated with psychiatric and neurological disorders, as well as the oxidative stress, inflammatory biomarkers and metabolic state in general, through the probiotic effects on CNS bidirectional circuits are mediated by the gut–microbiota–brain axis [48, 49]. Different probiotics have been investigated for psychiatric and neurological disorders; however, Bifidobacterium and Lactobacillus have been shown to be more effective [50]. The literature evidence shows that increased inflammation is associated with anxiety-like behavior [43–45; 51–53]. In general, the mechanisms underlying the effects of the microbiota on the CNS are multifactorial (immunologic, endocrine and neural), but these effects are believed to principally occur via the generation of bacterial metabolites [54]. The mechanisms of action of probiotics involve colonization of intestinal microflora; competitive exclusion of pathogens and bacteriocin production; modulation of enzymatic activities and production of volatile fatty acids. In addition, probiotics increase mucin production and cell adhesion in the gut [55]. Thus, probiotic metabolites are able to interact with the brain-gut axis and play a role in behavior [55].

Specifically referring to each probiotic strain, a study carried out on mice has shown that the administration of a mixture of Lactobacillus, including Lactobacillus reuteri, can increase the expression of tight junction proteins in intestinal epithelial cells [56, 57]. In humans, Lactobacillus reuteri has also been proven effective in disorders of the early stages of life such as colic or disorders characterized by excessive crying, which affects 10–30% of newborns [56]. Lactobacillus reuteri significantly reduced symptoms in acute uncomplicated diverticulitis, and it is shown by the reduced levels of inflammatory markers [57]. The mechanisms are probably its immunomodulating activity. Levels of IL-6, IL-8 and TNF-alpha are reduced after supplementation with different strands of Lactobacillus, while T-regulatory cells increase in number and activity [57].

The antimicrobial and immunomodulating power of Lactobacillus reuteri lies in the metabolites that it can produce [58]. Among these, one of the most important is reuterin, which in turn breaks down spontaneously into acrolein or a cytotoxic electrophile, capable of inhibiting a large amount of Gram-negative bacteria [58, 59], and others metabolites as acetic acid, ethanol and lactic acid [19]. Interestingly, Lactobacillus reuteri is also able to produce a biofilm [60]. The formation of biofilm is an important because it allows it to survive in the intestinal environment and to protect the epithelium from the adhesion of other pathogenic microorganisms [61].

On the other hand, Lactobacillus rhamnosus effectively alleviated bowel syndrome and reduced intestinal mucosal inflammation in inflammatory bowel disease [62, 63]. The anti-inflammatory activity also extended beyond the gut to reduce symptoms in patients with allergic diseases [64, 65] and atopic dermatitis [66]. Previous studies showed Lactobacillus rhamnosus pre-treatment reduced intestinal mucosal injury, gut microbiota dysbiosis, and sepsis mortality in a mouse model of cecal ligation and puncture (CLP) peritonitis [67]. Lactobacillus rhamnosus down-regulated several pro-inflammatory cytokines/chemokines, but also increased the survival rate in response to experimental sepsis in a study performed by Tsui et al. 2021 [68].

Finally, Bifidobacterium lactis has exhibited the highest β-glucosidase activity with strong acid tolerance in a recent study performed by Kim et al. 2019 [69] suggesting an enhanced immunomodulatory effect. Le Barz et al. 2018 [70] have showed an important reduction of cytokines after Bifidobacterium lactis treatment in animal model of obesity, as well prevention of obesity development and the reduction of associated intestinal and metabolic disturbances.

The decrease in oxidative stress in animals supplemented with probiotics indicates immunomodulatory and antioxidant activity provided by probiotic supplementation (see Figs. 4 and 6). Thus, probiotics provide health benefits, mainly by maintaining intestinal integrity. This assertion can be supported by the results obtained in this study, the reduction of inflammation and oxidative stress, the preservation of intestinal villi, the better behavioral response as well as the reduction of brain inflammation confirm the interaction between the gut–brain bidirectional axis, demonstrating how
Fig. 6 Heat map has been constructed to summarize the immunomodulatory effects of the three probiotic strains studied. IL-1, IL-6 and IL-10, as well as MPO and NO were grouped in a heat map. The color intensity shows greater expression of the corresponding protein. \( n = 5 \)
the maintenance of intestinal integrity provided by probiotic microorganisms prevented inflammation in brain tissue, ensuring greater health and homeostasis.

**Conclusion**

The probiotic microorganisms *Bifidobacterium lactis* (LACT GB™), *Lactobacillus rhamnosus* (RHAM GB™) and *Lactobacillus reuteri* (REUT GB™) showed efficient immunomodulatory activity, verified through the anti-inflammatory and antioxidant activity. In addition, probiotic supplementation was able to guarantee the integrity and the intestinal barrier function, even after the severe insult by LPS, where the modulation of the inflammatory process was verified, avoiding systemic inflammation. Finally, supplementation with the probiotic *Bifidobacterium lactis* (LACT GB™) had an effect on the behavior of the animals, being able to reduce anxiety related to the bidirectional interaction of the intestine–brain axis.

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**Authors’ Contributions** MM and GFAJ contributed to the conceptualization and design of the study; data curation; formal analysis and methodology; roles/writing—original draft. MRA, EC and LC were involved in the conceptualization and design of the study; methodology. HMB, NSM, LBR and RD helped in the conceptualization and design of the study; methodology; and data curation; CSS, APV, MR and FR contributed to the data curation; formal analysis; and methodology. FDP was involved in the conceptualization and design of the study; project administration; supervision; funding acquisition; writing—review and editing. All authors approved the final version submitted.

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**Data Availability** Data will be made available on reasonable request.

**Declarations**

**Consent to Participate** All authors listed have contributed sufficiently to the review to be included as authors, and all those who are qualified to be authors are listed in the author byline.

**Consent for Publication** The manuscript has been read and approved by all named authors, and we confirm that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the corresponding author is the sole contact for the Editorial process. He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

**Conflicts of Interest/Competing Interests** Gabbia Biotechnology are developing probiotics strains for commercial purposes. Gabriel Jesus, Fernanda Ramlov, Marina Rosseto and Ana Paula Voytena are members of Gabbia Biotechnology. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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