Chapter 41

Lactobacillus casei: Effects of its use against Pathogens (Parasites, Bacteria and Viruses) of Veterinary and Public Health Importance

Jair Millán-Orozco[1]*, Jersson Millán-Orozco[1], Antonio Martínez-Millán[2] and Liliana Aguilar-Marcelino[3]

[1]Laboratorio de Anatomía, Departamento de Ciencias Médico Veterinarias, División Regional de Ciencia Animal, Universidad Autónoma Agraria Antonio Narro-Unidad Laguna (UAAAN-UL). Periférico Raúl López Sánchez y Carretera a Santa Fe, Colonia Valle Verde, C.P. 27054, Torreón, Coahuila, México
[2]Programa de Licenciatura en Medicina Veterinaria y Zootecnia, División Regional de Ciencia Animal, Universidad Autónoma Agraria Antonio Narro-Unidad Laguna (UAAAN-UL). Periférico Raúl López Sánchez y Carretera a Santa Fe, Colonia Valle Verde, C.P. 27054, Torreón, Coahuila, México
[3]Centro Nacional de Investigación Disciplinaria en Salud Animal e Inocuidad (CENID-SAI), Instituto Nacional de Investigaciones Forestales, Agrícolas y Pecuarias (INIFAP). Carretera Federal Cuernavaca-Cuautla No. 8534, Colonia Progreso, C.P. 62390, Jiutepec, Morelos, México
*Corresponding author: jmillan.orozco@uaaan.edu.mx

ABSTRACT

Bacteria of the genus *Lactobacillus* and their application in both humans and animals have become very important. The different species of this bacterium, but especially *Lactobacillus casei*, has proven to be a promising strategy for the control of pathogens, as the different routes of administration have demonstrated the ability to stimulate a good humoral and cellular immune response in infected hosts both naturally and experimentally. In addition, *Lactobacillus casei* in humans, rodents and production animals can protect against certain parasitic, bacterial and viral infections, decreasing pathogen loads, establishment and colonization, as well as intestinal lesions, and increasing weight gain and survival. This chapter presents evidence of the above, concerning the study of highly relevant issues related to the use and administration of *Lactobacillus casei* in production animals, humans and animal models for the control of protozoan parasites and helminths, as well as against bacteria and viruses.

KEYWORDS
Bacteria, Helminths, *Lactobacillus casei*, Probiotics, Protozoa, Viruses.

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INTRODUCTION

In recent decades there has been an interest in the role of probiotic bacteria in the prevention of digestive disorders (Elmer et al., 2001; Pereg et al., 2005), therefore different agents have been used among which lactic acid bacteria, particularly *Lactobacillus* species, are the commonly used probiotics (Mombeli and Gismondo, 2000). This bacterium has been shown to be an immunostimulant (Bautista-Garfias et al., 2005), as it has a protective response against numerous infections in both animals and humans (Ashraf et al., 2005; Bautista-Garfias et al., 2002; Bautista-Garfias et al, 2005; Hori et al., 2001; Maldonado and Perdigón, 2006; Sato, 1984; Vercruysse et al., 2007), which is why it has been proposed as an alternative for disease control due to its capacity to increase non-specific immunity (Bautista-Garfias et al., 1999; Masihi, 1994). In addition, probiotics can provide benefits to both animal and human health when administered in adequate amounts (Boros et al., 2022; Hill et al., 2014).

Bacteria of the genus *Lactobacillus* comprise about 180 Gram-positive bacteria (Haakencen et al., 2009), and one of the main mechanisms of action is related to their ability to compete with pathogens for adhesion sites, improve the activity of the intestinal mucosal barrier, produce microbial agents and regulate host immune responses (Butell, 2014; Donelli et al., 2013). These lactic acid microorganisms are used in the dairy industry, as they provide a better taste in dairy products and increase their nutritional properties (Martínez-Gómez et al., 2006), as well as improve intestinal microflora when administered to animals and humans.

Lactobacillus casei (*L. casei*) and its Effects on Immunity

It has been demonstrated that the administration of *Lactobacillus casei* (*L. casei*) in mice stimulates an immuno-protective response against several parasites (Bautista et al., 2008; Bautista-Garfias, 2004;), in addition to stimulating the production of interleukin IL-12 and interferon-gamma (INF-γ) (Kato et al., 1999), thus promoting the expression of cytokines and the maturation of surface markers on the surface of dendritic cells (Christensen et al., 2000) through the stimulation of Toll-like receptors 2 (TLR2) (Matsuguchi et al., 2003), which similarly occurs in *Babesia bovis*-infected cattle, generating a Th1-type immune response associated with the production of INF-γ, interleukin IL-12, nitric oxide, and immunoglobulin IgG2 (Brown and Palmer, 1999; Shoda et al., 2000).

In mice treated with *L. casei*, an increase in the number of mononuclear cells in the stroma of the intestinal villi was observed (Bautista-Garfias et al., 1999), although it was not determined whether these cells were lymphocytes or macrophages, the findings suggest that *L. casei* treatment enhances the local immune response, also improving the amount of major histocompatibility complex class two antigens (MHC-II) on peritoneal macrophages (Kato et al., 1988). Regarding INF-γ in serum from *L. casei* treated animals showed that it is a potential activator of macrophages (Suzuki et al., 1988) and stimulates antigen presentation to enhance MHC gene expression (Gaszynska et al., 1993).

In addition, colonization of *L. casei* in the gut and processing of dead *Lactobacillus* by macrophages in local immune tissues and antigen presentation to Th1 cells may produce IL-2 to activate B cells and T cells, as well as INF-γ, which probably activates macrophages in a pathway in which these cells rapidly process antigens enhancing the acquired immune response, as these macrophages also produce nitric oxide and probably promote an inflammatory response in the gut (Bautista-Garfias et al., 2001).

Intranasal administration of *L. casei* in mice has been shown to induce the production of cytokines such as INF-γ, interleukin IL-12, and tumor necrosis factor-alpha (TNF-α) (Hori et al., 2001), suggesting that inoculation with *L. casei* enhances cell-mediated immunity in the respiratory tract and protects against viral infections such as influenza. It has been proposed that *L. casei* is involved in antibody production, however, some of the mechanisms have not yet been elucidated. It is proposed that the dendritic cells activated by *L. casei*, futherly process the antigens of some protozoa and induce the production of specific IgG1 and IgG2 antibodies (Bajer et al., 2003), and this probably may occur due to the presence of an increased number of memory B cells (Bautista-Garfias et al., 2015). *L. casei* is known to stimulate the production of Toll-like receptors (Maldonado and Perdigón, 2006; Vizoso et al., 2009), as well as modulate adaptive cellular and humoral immunity, leading to an enhanced acquired immune response against particular antigens (Bautista and Mosqueda, 2005; Ferwuerda et al., 2010).

Studies have suggested that probiotics can decrease the pathogenicity of parasites and, as a consequence, influence the course of parasitic infections (Berrili et al., 2012). In this regard, the main mechanisms of action of probiotics are related to their ability to compete with pathogens for adhesion sites, enhance the activity of the mucosal-intestinal barrier, produce antimicrobial agents and regulate host immune responses (Butel, 2014; Donelli et al., 2013). In addition, it regulates anti-inflammatory cytokine (IL-10) levels and increases the number of mucus-producing epithelial cells (McClemens et al., 2013). The mechanism behind immunomodulation involves interactions between *L. casei* and gut-associated lymphoid tissue (GALT), which is an important local immune compartment, thus probiotics such as *L. casei* can modulate the activity of several cells, such as erythrocytes, dendritic cells (DCs) and T-cells, and increase protection against intestinal infections (Boros et al., 2022; De Le Blanc et al., 2007; Friedrich et al., 2017; Randazzo and Contamagna, 2005; Sanchez et al., 2017).

In young animals (bovines) of different ages, *in vitro* studies, have shown that *L. casei* has the ability to produce nitric oxide in bovine monocytes, and specially shows higher production of nitric oxide within 4-6-month-old animals. Studies also suggested that *L. casei* can be used in *in vivo*, to stimulate innate immunity, specifically in young animals (Bautista-Garfias et al., 2016).

Chemical Properties of *Lactobacillus casei*

The hydrophilic nature of the genus *Lactobacillus*, regardless of species, has been reported in several studies (Andreu et al., 1995; Cuperus et al., 1993; Harty et al., 1993; Reid et al., 1992). In addition, it has a maximum affinity for an acidic solvent, such as chloroform, and a low affinity for a basic solvent, such as ethyl acetate, confirming the hydrophilic properties of its cell surface (Pelletier et al., 1997).

Lactobacillus casei produces biosurfactants, which are surface-active microbial compounds with antimicrobial and antioxidant activities with a wide range of physiological properties including methyl palmitate (2,5-O methyl rapmnofuranosyl palmitate) (Mouafo et al., 2021). Although there is little work on the structural characterization of *L. casei* biosurfactants, they have been reported as a mixture of proteins, polysaccharides, phosphates and lipids (Ferreira et al., 2017; Madhu and Paprulla, 2013; Sharma and Saharan, 2016).

Effects of *L. casei* on Parasites Affecting Animal Health

L. casei against *Babesia bovis* (*B. bovis*) and *Babesia bigemina* (*B. bigemina*)

Bautista-Garfias et al, (2008) evaluated the effectiveness of *L. casei* in conjunction with a vaccine against *Babesia bovis* and *Babesia bigemina* resulting in an increase in the agglomerated cell volume and a better rectal temperature in those animals where *L. casei* was applied intramuscularly, also the level of anti-*Babesia* antibodies was found higher after 10 days of treatment, as well as a better production of INF-γ compared to the control groups, indicating that the

inoculation of *L. casei* two days before vaccination improves the efficiency of the bivalent vaccine. Subsequently, the same research group conducted a second study evaluating the simultaneous vaccination of cattle with *L. casei* and the bivalent vaccine against bovine Babesiosis under field conditions. A decrease in rectal temperature was recorded 13 days after exposure to *Babesia*-infected ticks, as well as an increase in the average percentage of agglomerated cell volume was recorded between 13 and 15 days. Also, a lower percentage of parasitized erythrocytes was observed 12-14 days after exposure to infected ticks, while anti-*Babesia* IgG antibody levels were higher 20 days after confrontation (Bautista-Garfias et al., 2012). Finally, a third *in vitro* study was developed by Bautista-Garfias et al, (2015), which evaluated the levels of specific IgG1 and IgG2 antibodies against *B. bovis* and *B. bigemina* in cattle co-immunized with *L. casei*, observing that the levels of IgG1 and IgG2 antibodies were found higher in animals co-immunized with *L. casei* and the bivalent vaccine between 15-30 days of post-confrontation, in addition, the rectal temperature remained within normal parameters, and the percentage of parasitized erythrocytes was found lower after 24 hours in vitro.

L. casei* against *Eimeria acervulina, E. maxima* and *E. tenella

So far, there is only one work available in the scientific literature on the use of *L. casei* against coccidia of the genus *Eimeria* by Bautista-Garfias et al., (2003) who compared its effectiveness with that of a commercial vaccine in chickens. The results showed that the daily weight gain was equal to that produced by the commercial vaccine compared to the control groups (untreated-infected; untreated-infected-untreated). In addition, the average number of oocysts was lower and very similar to that of the vaccinated group after 5-8 days of post-infection. Similarly, the average number of intestinal lesions at necropsy (33 days of post-infection) was lower in the duodenum, jejunum, and cecum.

***L. casei against Haematobia irritans* (*H. irritans*)**

As with the previous parasitic genus, there is only one study carried out by Bautista-Garfias et al., (2004), in which *L. casei* was used in conjunction with incomplete Freund's adjuvant (IFA) and immunized with intestinal antigens of the horn fly (*H. irritans*). The results showed that the percentage reduction of oviposited eggs of each fly was lower compared to the immunized group without *L. casei*, and IgG antibody levels were higher in the group immunized with *L. casei* and IFA.

Table 1: *L. casei* against parasites of concern in production animals

Parasites	Species	Authors	Results
B. bovis	Cattle (*Bos taurus taurus*)	Bautista et al., 2008; Bautista-Garfias et al., 2012; Bautista-Garfias et al., 2015	Increased serum IgG1 and IgG2 levels.
B. bigemina	Cattle (*Bos taurus taurus*)	Bautista et al., 2008; Bautista-Garfias et al., 2012; Bautista-Garfias et al., 2015	Increased serum IgG1 and IgG2 levels.
E. acerbulina	Broiler chickens (*Gallus gallus domesticus*)	Bautista-Garfias et al., 2003	Increase in weight gain; decrease in oocyst excretion; decrease in intestinal lesions; increase in chick survival.
E. maxima	Broiler chickens (*Gallus gallus domesticus*)	Bautista-Garfias et al., 2003	Increase in weight gain; decrease in oocyst excretion; decrease in intestinal lesions; increase in chick survival.
E. tenella	Broiler chickens (*Gallus gallus domesticus*)	Bautista-Garfias et al., 2003	Increase in weight gain; decrease in oocyst excretion; decrease in intestinal lesions; increase in chick survival.
H. irritans	Cattle (*Bos taurus taurus*)	Bautista-Garfias et al., 2004	Reduced oviposition of adult flies; increased serum IgG levels.

Effects of *L. casei* on Parasites Affecting Public Health

***L. casei* against *Babesia microti* (*B. microti*)**

Oral and intraperitoneal administration of *L. casei* against the intracellular protozoan *Babesia microti* (*B. microti*), which affects humans, was evaluated using mice as an animal model, and it was observed that mice treated with *L. casei* showed a significant reduction in the percentage of parasitized erythrocytes compared to untreated mice. Infection with *B. microti* and treated with *L. casei* orally or intraperitoneally, seven days before infection, was lower from 17 days post-infection and remained so until the end of the study (day 31). The protective response showed better results when *L. casei* was administered three days before or the same day of infection, demonstrating that the percentage of parasitemia, according to the number of infected erythrocytes, was less than 5% throughout the study, especially when the *L. casei* bacteria were viable (Bautista-Garfias et al., 2005). Subsequently, a study was conducted to evaluate the capacity of viable and dead *L. casei* in mice challenged with erythrocytes infected with *B. microti*. The results showed that mice treated with *L. casei* had a lower average number of parasitized erythrocytes compared to the control group (untreated), and reported low (19-59kDa) and high (63-111kDa) molecular weight *L. casei* components. The results suggest that *L. casei* can induce a protective immune response with both live and dead *L. casei* probiotics (Bautista et al., 2008).

***L. casei* against *Cryptosporidium parvum* (*C. parvum*)**

One of the first studies evaluating the use of probiotics for the control of cryptosporidiosis in humans was carried out by Pickerd and Tuthill (2004), using daily treatment with *L. casei* (Shirota) for 10 days, in which nausea, diarrhea and abdominal pain were reduced, allowing the patient (12-year-old girl) to return to normal activities.

Subsequently, to evaluate the effect of *L. casei* against *C. parvum*, rats were used as a model for this purpose, administering a conjugate of *L. casei* two days before infection, where they measured weight gain, parasite load, damage to the intestinal mucosa and expression of muco-intestinal cytokines. However, the results showed that the daily administration of a conjugate of *L. casei* was ineffective in eradicating the parasite compared to the biological model. One of the possible explanations for the lack of success in this study could be that the conjugate contained in addition to *L. casei*, *L. bugaricus*, *L. acidophilus*, *L. plantarum*, *B. longum*, *B. breve*, *B. infantis*, *S. thermophilus*, which probably could have led to bacterial antagonism, thus reducing the effectiveness of the conjugate (Guitard et al., 2006).

One of the applications of *L. casei* against *C. parvum* was carried out in mice using *C. parvum*-P23 protein inserted into *L. casei* (Zhang strain). The results showed that oral administration of this recombinant protein increased the levels of cytokines IL-6 and interferon gamma (INF-γ), in addition to increasing IgA antibody levels during days 28-35 days, it also increased the IgG antibody levels during 21-42 days of post-infection compared to the control groups, making clear its immunogenic capacity (Geriletu et al., 2011).

***L. casei* against *Entamoeba invadens* (*E. invadens*)**

The effectiveness of the use of *L. casei* against *Entamoeba* protozoa was tested against *E. invadens*, which is very acceptable model for carrying out the evaluations against *E. histolytica*. The results showed that the survival rate of cells infected with *E. invadens* trophozoites was higher in the group where *L. casei* was used, achieving 95% survival in vitro (Sarjapuram et al., 2016).

***L. casei* against *Giardia lamblia* (*G. lamblia*)**

There are few evidence on the application of *L. casei* for the control of *G. lamblia*, however, in a first study in mice infected with trophozoites, it was observed that the oral application of *L. casei* decreased the number of cysts produced and eliminated in the feces by *G. lamblia*, and the number of trophozoites in the small intestine of mice was lower 3-7 days of post-infection. Necropsy findings showed that mice treated with *L. casei* had fewer atrophied villi and fewer infiltrating cells in the small intestine compared to controls. These results demonstrated that *L. casei* minimized *G. lamblia* infection by preventing the adhesion of trophozoites on the intestinal mucosal surface, suggesting that *L. casei* is effective and safe for preventing and treating *G. lamblia* infection (Shukla et al., 2008).

Subsequently, biochemical and histopathological parameters were evaluated in malnourished mice infected with *G. lamblia* and supplemented with *L. casei*. Histological, morphological and cell membrane alterations of the intestinal microvilli showed that *L. casei* supplementation decreased intestinal mucosal damage in the malnourished mice compared to the lesions produced in the control group. Serum total protein, albumin and globulin levels were higher during 7-17 days of post-treatment compared to the malnourished mice infected with *G. lamblia* but not supplemented, and the number of cysts sheds in the feces, as well as the number of trophozoites established in the small intestine was lower in the supplemented and infected animals compared to the controls. The results make it clear that the administration of *L. casei* has an anti-giardiasis effect in vivo, as it modulates and prevents the colonization, multiplication and encystation of *G. lamblia* trophozoites, thus reducing the duration and severity of giardiasis in the murine model (Shukla and Sidhu, 2011).

Subsequently, supplementation was carried out for 7 days with different probiotics of the *Lactobacillus* genus, to counteract the effects of Giardiasis in mice infected with *G. lamblia* trophozoites. The results indicated that mice treated with *L. casei* and infected mice showed a lower number of cysts eliminated in the feces from the first-day post infection until the end of the study, and that the groups treated with *Lactobacillus* eliminated a higher number of colony-forming units (CFU/mL) in the feces. Similarly, mice treated with *L. casei* showed a significant reduction in the number of trophozoites colonizing the small intestine, suggesting that the use of this type of probiotic is effective for the control of murine Giardiasis (Goyal et al., 2011).

Recently, the effect of the use of *L. casei* on parasitological and pathological parameters of hamsters experimentally infected with *G. lamblia* was evaluated. Parasitological parameters showed that, in animals treated with *L. casei*, the number of cysts was reduced by up to 55% after three days of treatment, achieving 100% cyst reduction after 21 days, while animals treated with metronidazole showed 49% reduction three days of post-treatment, achieving a maximum of 80% cyst reduction up to 30 days post-treatment. Pathological parameters showed marked improvement of intestinal villi with mild duodenitis and mild edema compared to moderate active duodenitis in terms of loss of villus structure, with edema of the lamina propria with moderate inflammation and cellular infiltration, including plasma cells and lymphocytes and moderate numbers of neutrophils present in the metronidazole treated group. These results demonstrate the potential therapeutic effect of *L. casei* against experimental giardiasis in hamsters (Shady et al., 2023).

***L. casei* against *Giardia intestinalis* (*G. intestinalis*)**

A group of researchers from India conducted several studies on the use of *L. casei* against protozoa of the genus *Giardia*, specifically against *G. intestinalis*. In a first study, they used daily administration of *L. casei* as a supplement for 7 consecutive

days to control infection in mice, evaluating the integrity of the intestinal microvilli membrane, demonstrating that those animals supplemented with *L. casei* and infected with *G. intestinalis* showed less histological and morphological damage to the intestinal mucosa, thus reducing the damage caused by the infection (Shukla et al., 2012).

Subsequently, the use of *L. casei* alone as well as in conjunction with *G. intestinalis* anti-protozoal drugs was evaluated in mice infected with trophozoites and treated at 24 hours of post-infection. The results showed that in animals infected and treated with *L. casei*, as well as in those infected + *L. casei* + albendazole reduced the number of oocysts and trophozoites and restored the intestinal mucosal architecture, with an increase in crypts and villi, and showed moderate inflammation in the lamina propria, suggesting the effectiveness of *L. casei* alone and albendazole in reducing the effects of this parasitosis (Shukla et al., 2013). In addition, oral administration of *L. casei* was evaluated to assess the intestinal physiology and morphology of malnourished mice infected with *G. intestinalis*. The findings indicate that the use of *L. casei* in malnourished and infected animals decreased the number of cysts 24 hours of post-infection, increased small intestinal mass, increased small intestinal enzyme activity (sucrase, lactase, maltase, alkaline phosphatase) and improved intestinal microvilli morphology (Shukla et al., 2013).

Finally, the symbiotic effect of *L. casei* + Inulin was evaluated in malnourished mice infected with *G. intestinalis*. The findings reported showed that those infected animals in which the symbiotic effect of *L. casei* + Inulin was evaluated presented a better intestinal mass and a lower amount of trophozoites. Moreover, the same group of animals presented higher levels of IL-10 and IL-6, nitric oxide, IgG and IgA in both serum and intestinal fluid; in addition, they presented better morphology and orientation of intestinal microvilli. However, further studies were suggested to validate its use in patients (naturally infected humans due to the difference in the intestinal microbiota of mice and humans) (Shukla et al., 2019).

Table 2: *L. casei* against protozoan (intestinal) parasites of public health concern

Parasites (protozoa)	Species	Authors	Results
C. parvum	Humans (*Homo sapiens*)	Pickerd y Tuthill, 2004	Reduction of nausea, diarrhea and abdominal pain.
	Rats (*Rattus norvegicus albinus*)	Guitard et al., 2006	No significant effects (weight gain, parasite load, intestinal mucosal damage and cytokine expression).
	Mice (*Mus musculus*)	Geriletu et al., 2011	Increased IgA and IgG levels, as well as IL-6 and INF-γ levels.
E. invadens	*In vitro* cell culture	Sarjapuram et al., 2016	Increased survival of infected cells.
G. lamblia	Mice (*Mus musculus*)	Shukla et al., 2008	Decrease in atrophied villi and infiltrating cells.
	Mice (*Mus musculus*)	Sukla y Sidhu, 2011	Decreased intestinal damage; increased total protein, albumin and globulin in serum; decreased cysts in feces and trophozoites in intestine.
	Hamsters (*Mesocricetus auratus*)	Shady et al., 2023	Decreased cysts; moderate inflammation and cellular infiltration in intestine; moderate numbers of plasma cells, lymphocytes and neutrophils.
G. intestinalis	Mice (*Mus musculus*)	Shukla et al., 2012	Decreased histological and morphological damage to the intestine; increased membrane integrity of microvilli.
	Mice (*Mus musculus*)	Shukla et al., 2013	Reduction of cysts and trophozoites; restoration of intestinal mucosa with increased crypts and villi; moderate inflammation of lamina propria.
	Mice (*Mus musculus*)	Shukla et al., 2013	Decrease of cysts; increase of intestinal mass and enzyme activity; improvement of microvilli.
	Mice (*Mus musculus*)	Shukla et al., 2019	Improved intestinal mass; decreased trophozoites; increased levels of IL-6 and IL-10, nitric oxide, IgA and IgG in serum and intestinal fluid.

***L. casei* against *Plasmodium chabaudi* (*P. chabaudi*)**

Martínez-Gómez et al., (2006) evaluated the ability of *L. casei* to increase resistance to the protozoan *P. chabaudi* in mice inoculated with previously infected splenocytes. The results of the study showed that mice treated once or twice with *L. casei* prior to infection had a lower percentage of infected erythrocytes compared to groups that were only infected with splenocytes and not given *L. casei*. The authors concluded that administration of *L. casei* to mice increases resistance to *P. chabaudi* infection, resulting in low parasite loads, decreased viability of the protozoan, and increased serum nitrous oxide.

***L. casei* against *Plasmodium berghei* (*P. berghei*)**

Recent studies evaluated the effect of *L. casei* probiotic combined with chloroquine therapy to reduce the adverse effects of *P. berghei* malaria in the mouse model (Mahajan et al., 2021). The results of this research showed that the group of animals treated exclusively with *L. casei,* reduced the percentage of parasitemia compared to the control group; however, the group treated with *L. casei* + Chloroquine and infected with *P. berghei* showed a greater reduction in the percentages of parasitemia from the first-day of post-infection until the end of the study. When liver histology was performed, a reduction in periportal inflammation and hemosiderosis was also observed when the animals were treated with *L. casei* alone, however, in those animals treated with *L. casei* + Chloroquine, there were fewer liver lesions. The above results show that, when *L. casei* is applied together with a chemical therapy (chloroquine), a synergistic effect was achieved for malaria control in a mouse model, reducing parasite counts and improving the pathological changes that appear after *P. berghei* infection.

Subsequently, a further investigation was carried out to evaluate the effects of the use of probiotics *L. casei* and *B. longum* separately and together, evaluating the level of parasitemia, the composition of the intestinal microbiota, expression of regulatory T lymphocytes, INF-γ and TNF-α in mice infected with *P. berghei*. The results of the study showed that there was a significant difference in the level of parasitemia in animals treated with probiotics compared to the positive control group.

The degree of parasitemia was lower in the groups where the probiotic *L. casei* or *L. casei* + *B. longum* was applied intraperitoneally during the first 5 days of post-infection compared to the control group. The survival rate remained constant (100%) in the *L. casei* + *B. longum* group throughout the study, while in the *L. casei*-only group, the survival rate was 60-100%, compared to 40% survival in the positive control group. The ring-shaped parasites of the protozoan *P. beghei* were observed from day 2 in the control group, while in the treated groups they appeared 4-6 days of post-infection. The level of expression of regulatory T-lymphocytes was higher in the *L. casei* and/or *B. longum* treated animals, either together or separately; however, the expression levels of cytokines INF-γ and TNF-α, and the histological changes (ulceration, erosion and inflammation) in the colon of the mice were not different compared to those of the positive controls. The mechanism involved in the reduction of parasitemia has so far not been fully elucidated. However, immuno-modulatory properties such as enzymes, antimicrobial peptides, and short-chain fatty acids have been attributed, which may play an important role against *P. berghei* infections (Fitri et al., 2023).

***L. casei* against *Trypanosoma cruzi* (*T. cruzi*)**

Inoculation of *L. casei* to evaluate its oral and intraperitoneal effectiveness against *T. cruzi* infection in experimentally infected mice was carried out by Bautista et al., (2008). A marked reduction in the number of blood parasites (trypomastigotes) was recorded in both the oral and intraperitoneal *L. casei* treated groups compared to the control group from day 6 to day 28 of post-infection. The average total number of blood trypomastigotes recorded between days 10-28 of post-infection was 3,820 for the group treated with *L. casei* orally, while an average of 1,842 was obtained in the group treated with *L. casei* intraperitoneally.

This indicates that intraperitoneal treatment with *L. casei* was more effective in generating resistance to *T. cruzi* infection in mice. The protection conferred against *T. cruzi* was due to the activation of the innate immune response by *L. casei*; although the intraperitoneal route of application was more effective than the oral route, both showed resistance against infection when compared to the control group (saline).

***L. casei* against *Toxoplasma gondii* (*T. gondii*)**

During the first decade of this century, Martínez-Gómez et al., (2009) evaluated the protection against the formation of brain cysts produced by the protozoan *T. gondii* in mice immunized with cytoskeleton proteins of the parasite in question and the application of *L. casei* as an adjuvant. The percentage reduction in brain cysts was 77% for the group treated with the cytoskeleton proteins and *L. casei* as adjuvant, while the group treated with *L. casei* alone reduced the percentage of brain cysts by 44%, compared to a 6% reduction in brain cysts in the animals treated with phosphate-buffered saline (PBS) alone. The results suggest that the administration of cytoskeletal proteins, using *L. casei* as an adjuvant, is a good vaccine candidate for the control of toxoplasmosis in mice (Martinez-Gomez et al., 2009).

Very recently, a second study evaluated the potential immunobiotic and paraprobiotic effect of *L. casei* in a murine model of systemic toxoplasmosis (Salas-Lais et al., 2020). Among the results of the aforementioned work, a reduction in parasite load (tachyzoites/mL), activation of peritoneal macrophages, as well as inflammatory cytokines (INF-γ, IL-6, TNF-α), and an increase in the expression of monocyte chemoattractant protein-1 (MCP-1) were recorded. Moreover, an increase in the percentage of B-lymphocytes, lymphocytes, natural killer cells (NKC), TCD4+, and TCD44+ lymphocytes were also observed. The survival rate remained constant at 90-100% for the first nine days of post-infection. The authors concluded that the application of viable (immunobiotic) and dead (paraprobiotic) *L. casei* bacteria demonstrated stimulation of the immune system, leading to the destruction of tachyzoites by producing intracellular oxide (Salas-Lais et al., 2020).

***L. casei* against *Trichinella britovi* (*T. britovi*)**

Recently, the effect of *L. casei* against *T. britovi* was evaluated, as until then there were no reports on the effect of probiotics on *Trichinella* species other than *T. spiralis*. For this purpose, mice were infected with 100 larvae per animal. The results recorded showed that in animals treated with *L. casei*, fewer larvae and adults were recovered both at nine-and thirty-

two-days of post-infection. These findings clearly show the potential negative effect on the development of this intestinal nematode, although the exact mechanisms behind this process need to be further investigated, however, the administration of *L. casei* is effective in reducing the parasite load, especially in adults of *T. britovi* (Boros et al., 2022).

Table 3: *L. casei* against haemoprotozoan and brain parasites of public health significance

Parasites (protozoa)	Species	Authors	Results
B. microti	Mice (*Mus musculus*)	Bautista-Garfias et al., 2005; Bautista et al., 2008	Reduction of parasitized red blood cells.
P. chaboudi	Mice (*Mus musculus*)	Martínez-Gómez et al., 2006	Reduction of infected red blood cells, parasite loads anc viability of protozoa; increase in serum nitrous oxide.
P. berghei	Mice (*Mus musculus*)	Mahajan et al., 2021	Decreased percentage of parasitemia; reduction in periportal inflammation.
	Mice (*Mus musculus*)	Fitri et al., 2023	Decreased parasitemia; increased regulatory T-lymphocytes, as well as INF-γ and TNF-α; reduced intestinal histological changes.
T. cruzi	Mice (*Mus musculus*)	Bautista et al., 2008	Reduction of blood parasites (trypomastigotes).
T. gondii	Mice (*Mus musculus*)	Martínez-Gómez et al., 2009	Reduction of brain cysts.
	Mice (*Mus musculus*)	Salas-Lais et al., 2020	Reduction of parasite load; activation of peritoneal macrophages, Il-6, INF-γ and TNF-α, increase of B lymphocytes, natural killer cells (NKC), CD4 and TCD44 T lymphocytes.

***L. casei* against *Trichinella spiralis* (*T. spiralis*)**

Bautista-Garfias et al., (1999) conducted the first study to evaluate the effect of viable *L. casei*, administered intraperitoneally, to induce resistance in mice infected with *T. spiralis*. Their results showed that the percentage reduction of adult nematodes in the intestine at 5 days of post-infection was 70-88%, while the reduction of larvae per gram of muscle tissue at 30 days of post-infection was 46-84% in those animals treated with *L. casei*, as well as an increase in intestinal villi size, a higher number of mononuclear cells in the duodenum, and an increase in INF-γ.

Subsequently, De Waard et al., (2001), administered *L. casei* to rats infected with *T. spiralis* two weeks before infection and for 5 days of post-infection, evaluating immunological parameters, and immunoglobulins. Oral administration of *L. casei* increased IgG2b concentrations, concluding that IgG2b is associated with Th1 immune activity, thus playing an important role in immunomodulatory effects in animals with oral administration of *L. casei* and infected *T. spiralis*.

A second study was conducted by Bautista-Garfias et al., (2001), evaluating the ability of orally administered *L. casei* live and dead probiotics, in which adult parasite reduction percentages of 53-58% were obtained when the *L. casei* probiotics were alive, while adult parasite reduction of 44% was obtained when the *L. case*i probiotics were dead. The percentage of larvae recovered in muscle tissue was 70% in mice treated with live *L. casei*, while 65% of larvae recovered were obtained in those animals treated with dead *L. casei* at 30 days of post-infection.

Martínez-Gomez et al., (2009) evaluated the effects of intraperitoneal administration of *L. casei* on the establishment of adult parasites and the production of anti-*T. spiralis* IgA. The results reported show that, in mice treated with *L. casei*, a significant reduction (86%) of adult parasites was established throughout the study (28 days), compared to the control group (without *L. casei*). Likewise, anti-*T. spiralis* IgA levels increased significantly in the group of animals treated with *L. casei*, indicating that inoculation with this probiotic induces protection and increases IgA production in intestinal fluid in mice infected with *T. spiralis*. A couple of years later, the same group of researchers evaluated intraperitoneal inoculation of *L. casei* to induce total protection against infection with low doses (10, 25, 50, 100 and 200 larvae) of *T. spiralis*. The results showed a decrease in the number of adult parasites in all groups treated with *L. casei*, and the percentage of reduction was higher in those animals treated with the lowest doses (10, 25 and 50 larvae).

Similarly, IgG and IgA levels were higher in the *L. casei* treated groups compared to the control groups, however, the highest serum IgG and intestinal IgA levels were obtained in those animals infected with doses of 50 and 200 larvae at both 4- and 10-days of post-infection. Finally, IL-4 levels were higher in all groups treated with *L. casei* and infected with *T. spiralis*, however, the highest IL-4 levels were obtained in the groups infected with 25 and 50 larvae, while at 10 days of post-infection, IL-4 levels were similar in the groups infected with 25, 50 and 200 larvae). All these results suggest that frequent treatment with *L. casei* in mice infected with low doses of *T. spiralis* induces total protection against infection (Martínez-Gómez et al., 2011).

The most recent study on the effects of *L. casei* against *T. spiralis* was carried out by (El Temsahy et al., 2015), administering *L. casei* orally against experimental intestinal trichinellosis and evaluating parasitological, immunological and histological parameters. The results obtained show that oral administration of *L. casei* was able to decrease the establishment of adult parasites in the intestine by 36, 23 and 31% after 5-, 12- and 17 days of post-infection, respectively. In addition, a higher weight was achieved in those animals treated with *L. casei* during the first 6 days of post-infection, compared to the control group.

In terms of immunological parameters, there was a significant increase in serum gamma interferon (INF-γ) levels during the first 12 days of post-infection in the group of animals treated with *L. casei* compared to the control group. Histological results showed that the intestinal villi were larger and the number of goblet cells increased, while tissue damage and inflammation were reduced in animals treated with *L. casei* orally, thus demonstrating the protective capacity of *L. casei* probiotics in mice experimentally infected with *T. spiralis*.

***L. casei* against *Trichuris muris* (*T. muris*)**

Although *L. casei* found to be effective against a wide range of parasites, there are reports in which it has generated susceptibility, such as the nematode *T. muris*, where oral administration to experimentally infected mice showed an increase in parasite load 22 days of post-infection. In addition, the application of viable *L. casei* reduced fecal IgA antibody levels, while the application of dead *L. casei* significantly decreased levels of INF-γ, TNF-α, IL-4, IL-5 and IL-13. The mechanisms of such evidence could be related to the deactivation of TNF-α-dependent Th2 effector response against *T. muris* due to a decrease of this cytokine that is induced by *L. casei* (Dea-Ayuela et al., 2008).

Table 4: *L. casei* against helminths of public health significance

Parasites (helminths)	Species	Authors	Results
T. britovi	Mice (*Mus musculus*)	Boros et al., 2022	Reduction in the establishment of larvae and adult nematodes.
T. spiralis	Mice (*Mus musculus*)	Bautista-Garfias et al., 1999	Reduction of larvae and adults in muscle tissue; increased size of villi; increased number of mononuclear cells; increased INF-γ.
	Rats (*Rattus norvegicus albinus*)	De Waard et al., 2001	Increased IgG2b levels.
	Mice (*Mus musculus*)	Bautista-Garfias et al., 2001	Reduction of larvae and adults in muscle tissue.
	Mice (*Mus musculus*)	Martínez-Gómez et al., 2009	Decreased adult parasites; increased IgA in intestinal fluid.
	Mice (*Mus musculus*)	Martínez-Gómez et al., 2011	Decrease of adult parasites; increase of IgA and IgG in serum and intestine; increase of IL-4.
	Mice (*Mus musculus*)	El Temsahy et al., 2015	Decreased adult parasites; increased weight gain; increased INF-γ; increased intestinal villi size; increased goblet cells; reduced intestinal tissue damage.
T. muris	Mice (*Mus musculus*)	Dea-Ayuela et al., 2008	Increased parasite load; reduced levels of fecal IgA, as well as INF-γ, TNF-α, IL-4, IL-5 and IL-13.

Effects of *L. casei* on bacteria affecting animal health

***L. casei* against *Brucella abortus* (*B. abortus*)**

Mohammadi and Golchin (2020), evaluated the protective effect of the OMP19 antigen of a virulent strain (544) of *B. abortus* as a vaccine candidate and produced within *L. casei* as a vaccine vector. The results of this study showed that application of the antigen in conjunction with *L. casei* increased IgG and IgA levels in the intestinal contents of mice, as well as increased serum levels of cytokines IL-2, IL-4, IL-10, INF-γ and decreased colony-forming unit counts, which was similar to findings produced by the vaccine strain IRIBA produced in calves.

***L. casei* against *Escherichia coli* (*E. coli*)**

To date, there are two studies available in the scientific literature on the use of *L. casei* against bovine mastitis caused by *E. coli*, using in vitro mammary epithelial cell culture and mouse models. Zheng et al., (2021) demonstrated *in vitro* that *L. casei* inhibits *E. coli* adhesion, as well as decreasing cellular desmosome damage, as well as decreases the lactate dehydrogenase enzyme and inflammatory cytokine expression (TNF-α, IL-1β and IL-6). Moreover, *L. casei* increased claudin-1, claudin-4, occludin and zonula occludens expression. Meanwhile, Li et al., (2024) demonstrated that, *L. casei* reduced cell apoptosis and the expression of TNF-α, IL-1β and IL-6; moreover, it suppressed enzyme phosphorylation. With respect to the mouse model, both studies showed that the use of *L. casei* by intramammary infusion reduced histological damage as well as the expression of inflammatory cytokines and increased the expression of claudin-3, occludin and ZO-1 proteins.

***L. casei* against *Staphylococcus aureus* (*S. aureus*)**

A group of researchers in Brazil conducted the first *in vitro* study, to evaluate the invasion capacity of *S. aureus* in bovine mammary epithelial cells, by Bourchard et al., (2013), in which *L. casei* was used as an antagonist to prevent such invasion. The results showed that the CIRM-BIA667 strain of *L. casei* reduced the cell internalization capacity of *S. aureus* by 60-80% during the first 2 hours of post-incubation, without affecting the morphology and viability of bovine mammary epithelial cells.

Subsequently, Souza et al., (2017) conducted a couple of in vitro studies using *L. casei* to prevent *S. aureus* internalization in bovine mammary epithelial cells. In the first study, the results demonstrated the inhibitory potential of *L. casei* (strain BL23) during the first 30 minutes of post-incubation, reducing cell internalization by more than 50%, generating an antagonism with *S. aureus*, thus preventing the production of adhesion proteins towards bovine mammary epithelial cells.

Finally, they evaluated the ability of *L. casei* strain BL23 to modulate the innate immune response of bovine mammary epithelial cells during *S. aureus* infection. The recorded results showed that *L. casei* strain BL23 decreased the expression of proinflammatory cytokines, including interleukins IL-6, IL-8, IL-1α and IL-1β, and TNF-α at 8 hours of post-infection, thus demonstrating the anti-inflammatory properties of *L. casei* (Souza et al., 2018).

Effects of *L. casei* on bacteria that affect public health

***L. casei* against *Mycobacterium bovis* (*M. bovis*)**

In order to reduce the risk of transmission of tuberculosis caused by *M. bovis* in humans, the effect of *L. casei* was evaluated in milk fermented with kefir grains from bovine tuberculosis-positive animals. The results obtained demonstrated the ability of *L. casei* to reduce the viability of M. bovis from 24 hours of post-fermentation, resulting in zero viability of *M. bovis* bacteria after 60 hours of post-fermentation (Macuamule et al., 2016).

Table 5: *L. casei* against bacteria of animal and public health importance

Bacteria	Species	Authors	Results
Brucella abortus	Mice (*Mus musculus*)	Mohammadi and Golchin, 2020	Increases IgG and IgA in intestinal fluid; increases serum IL-5, IL-4, IL-4, IL-10 and IFN-γ levels.
Escherichia coli	*In vitro* culture (Bovine mammary epithelial cells)	Zheng et al., 2021	Inhibits adhesion, decreases cellular desmosome damage; decreases lactate dehydrogenase and expression of TNF-α, IL-1β and IL-6.
	Mice (*Mus musculus*)	Zheng et al., 2021	Reduces histological damage and inflammatory cytokine expression; increases claudin-3, occludin and ZO-1 protein expression.
	In vitro culture (Bovine mammary epithelial cells)	Li et al., 2024	Reduces cell apoptosis and expression of TNF-α,, IL-1β and IL-6.
	Mice (*Mus musculus*)	Li et al., 2024	Reduces histological damage and inflammatory cytokine expression; increases claudin-3, occludin and ZO-1 protein expression.
Staphylococcus aureus	*In vitro* culture (Bovine mammary epithelial cells)	Bourchard et al., 2013	Reduces cell internalization (60-80%), does not affect cell morphology and viability.
	In vitro culture (Bovine mammary epithelial cells)	Souza et al., 2017	Reduces cell internalization (50%), prevents production of adhesion proteins.
	In vitro culture (Bovine mammary epithelial cells)	Souza et al., 2018	Decreases proinflammatory cytokines IL-6, IL-8, IL-1α and IL-1β, and TNF-α.
Mycobacterium bovis	Fermented milk	Macuamule et al., 2016	Decreases bacterial viability 24 h post infection.

Effects of *L. casei* on viruses affecting animal health

***L. casei* against Bovine Viral Diarrhea Virus (BVDB)**

There are few studies on the effects of the application of *L. casei* to control BVDV infections, however, the first study related to this topic was conducted by Bhuyan et al., (2018), who demonstrated in mice that *L. casei* containing recombinant pELX1-E2 antigen, and administered orally and intranasally induced significantly higher levels of intestinal mucosal IgA and serum IgG against E2 antigen, as well as a higher level of cellular immune response (INF-γ and IL-12) compared to intramuscular administration and controls.

L. casei strain W56 was later used to evaluate the effectiveness of the recombinant BVDV-E2 protein. This study demonstrated the effectiveness of *L. casei* in activating dendritic cells in Peyer's patches, as well as T-cell differentiation, enhancing B-cell proliferation, and promoting IgA differentiation by secreting specific anti-E2 antibodies, thus neutralizing BVDV activity. In addition, *L. casei* (strain W56) was able to induce cellular immune responses, and significant levels of IL-2, IL-12 and INF-γ (Th1), as well as IL-4 and IL-10 (Th2), and IL-17 (Th17) (Jia et al., 2020; Wuang et al., 2019). The above studies demonstrate that *L. casei* exhibits protection against BVDV, representing a promising control strategy.

***L. casei* against Newcastle virus**

Several studies on the effects of *L. casei* against Newcastle virus in broilers have shown that *L. casei* administered in the diet of broilers increases humoral immune response (IgG) (Alizadeh et al., 2017; Ogawa et al., 2006), increases body weight (Bautista-Garfías et al., 2011; Ju et al., 2021) and decreases mortality (Bautista-Garfías et al, 2011), reduces organ injury (lungs, liver, spleen, thymus and bursa of Fabricius), and improves serum IL-2 and INF-γ concentrations, as well as elevates IgA levels in intestinal fluid (jejunum) (Ju et al., 2021).

Effects of *L. casei* on Viruses Affecting Public Health

***L. casei* against Influenza viruses (H1N1, H3N2)**

The first report on the use of *L. casei* (Shirota strain) was carried out by Hori et al., (2001), administering *L. casei*

intranasally to activate the immune system of the respiratory tract of mice infected with the influenza virus (H1N1). The results showed that *L. casei* is able to induce the expression of IL-12, TNF-α and INF-γ in mediastinal lymph node cells and increase the survival (69%) of mice infected with influenza virus and treated with *L. casei*. These early findings suggested that intranasal administration of *L. casei* enhances the respiratory tract´s cellular immune response and protects against influenza.

Jung et al., (2017) evaluated the effectiveness of heat-killed, intranasally administered *L. casei* probiotics (strain DK128) to protect against influenza virus (H1N1 and H3N2) infection in mice. Protection against both influenza virus subtypes was recorded, with an increase in alveolar macrophages in the lungs and airways and early induction of specific antibodies, as well as a reduction in the levels of proinflammatory cytokines and innate immune cells. Moreover, increased body weight and survival rate (80-100%) of mice treated with *L. casei* intranasally were also observed.

Very recently, Spacova et al., (2023) evaluated the effect of a probiotic-based *L. casei* throat spray in human volunteers intending to reduce the negative effects of viral infections, including H1N1 and H3N2. Their results indicate that the administration of *L. casei* was able to colonize the throat of the patients, in addition to increasing the levels of nuclear factor (NK-κB) activation in monocytes and interferon regulatory factors (IRFs), demonstrating that *L. casei* could act as a therapeutic strategy against viral diseases of the respiratory tract, such as influenza.

Table 6: *L. casei* against viruses of animal and public health importance

Viruses	Species	Authors	Results
Bovine Viral Diarrhea Virus	Mice (*Mus musculus*)	Bhuyan et al., 2018	Increases IgA and IgG levels; increases cellular immune response (INF-γ and IL-12).
	Mice (*Mus musculus*)	Wang et al., 2019	Activation of dendritic cells; production of IgA and IgE; proliferation of lymphocytes; expression of INF-γ and IL-4.
	Mice (*Mus musculus*)	Jia et al., 2020	Dendritic cell activation; T-lymphocyte differentiation; B-lymphocyte proliferation and IgA differentiation; increased IL-2, IL-12, INF-γ, IL-4, IL-10 and IL-17.
Newcastle virus	Broiler chickens (*Gallus gallus domesticus*	Ogawa et al., 2006	Increases IgG levels.
	Broiler chickens (*Gallus gallus domesticus*	Bautista-Garfías et al., 2011	Increases body weight and decreases mortality.
	Broiler chickens (*Gallus gallus domesticus*	Alizadeh et al., 2017	Increases IgG levels.
	Broiler chickens (*Gallus gallus domesticus*)	Ju et al., 2021	Increases body weight; reduces organ damage (lungs, liver, spleen, thymus, and bursa of Fabricius); increases IL-2, INF-γ and IgA levels.
Influenza virus (H1N1, H3N2)	Mice (*Mus musculus*)	Hori et al., 2001	Induces IL-12, TNF-α and INF-γ expression in mediastinal lymph node cells, increases survival.
	Mice (*Mus musculus*)	Jung et al., 2017	Increased pulmonary alveolar macrophages and airways; induction of specific antibodies; reduced levels of proinflammatory cytokines and innate immune cells; increased body weight and survival.
	In vitro culture (Human cells)	Spacova et al., 2023	Throat colonization; increased levels of nuclear factor (NK-κB) activating monocytes and interferon regulatory factors (IRF's).

Conclusions and Perspectives

Since the first study twenty-five years ago, several researchers have used *L. casei* as a strategy for the control of some parasitosis, bacterial and viral diseases related to veterinary and public health. The results of all these studies have demonstrated the effectiveness of *L. casei* in regulating the immune response, reducing parasite loads and/or the establishment of adult parasites, reducing tissue damage in various organs, increasing the weight gains and animal survival.

Concerning the ability of *L. casei* to induce immune responses, *L. casei* stimulates both innate and acquired immunity against parasites, bacteria and viruses. However, the number of investigations for the control of different diseases in production animals is scarce, while they have been evaluated only in animal models or cell cultures. Therefore, it is still necessary to design more studies on the use of *L. casei* in animal production infected naturally and/or experimentally, but, above all, to increase the parameters to be evaluated and which are related to animal welfare and food quality.

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