Food Research International 45 (2012) 831–841

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Probiotics: An alternative strategy for combating salmonellosis Immune mechanisms involved

Natalia A. Castillo [a], Alejandra de Moreno de LeBlanc [a], Carolina Maldonado Galdeano [a,b], Gabriela Perdigón [a,b,*]

[a] Centro de Referencia para lactobacilos (CERELA), CONICET, Tucumán CP4000, Argentina
[b] Cátedra de Inmunología, Depto. de Microbiología, Universidad Nacional de Tucumán, Tucumán CP4000, Argentina

ARTICLE INFO

Article history:
Received 18 February 2011
Accepted 14 April 2011

Keywords:
Probiotic
Immune system
Salmonellosis

ABSTRACT

Salmonella produces infections of different nature and severity depending of many factors including the *Salmonella* serovar involved, strain virulence, infective dose, host animal species, age and immune status of the host. The treatments against *Salmonella* infections rely on supportive and antibiotic therapy to eliminate the pathogen, but the development of resistance by *Salmonella* to the antimicrobials most commonly used limits its efficacy. Other disadvantages of antibiotic treatments are that they can lead to acute diarrhea (antimicrobials normally induce an imbalance of intestinal bacterial flora) and may produce chronic toxicity. Considering this undesired consequences of antibiotics and because at the present there are no effective oral vaccines which protect against salmonellosis, scientists have been searching for alternative methods to control enteric infections. In the present review, probiotics are proposed as an attractive possibility to attend this concern. Probiotic are live microorganisms, which when administered in adequate amounts confer a health benefit on the host. In vitro and in vivo studies showed the effectiveness of probiotic administration in the prevention or in the treatment against *Salmonella* infection. There are several mechanisms by which probiotic strains might exert their effects. They include non immune mechanisms (stabilization of the gut mucosal barrier, competition for adhesion, secretion of antimicrobial substances, etc.) and the modulation of the mucosal and systemic immune responses. These mechanisms are species and/or strain specific. There are also evidences that in some cases, a mix of probiotic strains can be more useful than each strain alone against this infection. In addition, the presence of one or more probiotic strains in a fermented product can improve the beneficial properties of the probiotic strains involved. It was also reviewed the security of probiotics administration after *Salmonella* infection in healthy host and in immunosuppressed or babies hosts. Although, the major part of the researches were performed in animal models through in vivo assays or by in vitro studies using human cell lines, some studies carried out in humans to verify the probiotic effects were also addressed in the present review. Nevertheless, is of critical importance to perform more clinical trials in humans to validate the results obtained with each specific probiotic strain or probiotic product.

1. Introduction

Salmonellosis is a disease caused by a bacterium named *Salmonella,* in recognition of the work carried out by the American bacteriologist, D.E. Salmon. *Salmonella* causes several diseases that range from mild gastroenteritis to enteric (typhoid) fever, bacteraemia and septicemia (Mastroeni & Maskell, 2006).

Most persons infected with *Salmonella* develop diarrhea, fever, and abdominal cramps, 12 to 72 h after infection. The illness usually lasts 4 to 7 days, and most persons recover without treatment, even though they need several months before their bowel habits are entirely normal. However, in patients who develop enteric fever, the diarrhea may be so severe that the patients need to be hospitalized. In these patients, *Salmonella* spreads from the gut to the blood stream, and then to other body sites and can cause death if the patient is not treated promptly with antibiotics.

Salmonellosis also can lead to various chronic sequels; i.e. a small number of persons infected with *Salmonella* develop Reiter's syndrome, with pain in their joints, irritation of the eyes, and painful urination. It can last for months or years, and can lead to chronic arthritis which is difficult to treat. Antibiotic treatment does not make a difference in whether or not the person develops arthritis. Other sequels observed are endocarditis and appendicitis (Bell & Kyriakides, 2002).

Abbreviations: TLR, Toll-like receptor; IL, Interleukin; TNF, Tumoral necrosis factor; IFN, Interferon.

* Corresponding author at: CERELA-CONICET Chacabuco 145, San Miguel de Tucumán, Tucumán, T4000ILC, Argentina. Tel.: +54 381 4310465x129; fax: +54 381 4005600.
E-mail addresses: castillonaty@gmail.com (N.A. Castillo), demoreno@cerela.org.ar (A. de Moreno de LeBlanc), cmaldo@cerela.org.ar (C.M. Galdeano), perdigon@cerela.org.ar (G. Perdigón).

0963-9969/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.foodres.2011.04.031

This disease is rare in developed countries but in developing countries is relatively common, because of the poor sanitation facilities and untreated water supplies.

The immune compromised host is more vulnerable to get the disease, as well as the children less than five years old and the elderly people. The contamination with this pathogen is through the food. Foods contaminated by *Salmonella* usually does not develop any perceptible sensorial characteristics and can be derived from animals, fish and shellfish, fruit, vegetables, dairy product, or cereals. *Salmonella* have been reported in a variety of fresh products, such as coconut, cantaloupe melons, cilantro, paprika powder, mung bean seeds, cocoa beans, celery lettuce, parsley, scallions and strawberries (Bell & Kyriakides, 2002). Poultry and egg products have long been recognized as a source of *Salmonella* (Arthur, Jones, Fabri, & Odumeru, 2007; Lindhardt et al., 2009). Some studies have shown that multi antibiotic resistant *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) can be found in poultry and the poultry growing environment (Rajashekara et al., 2000). Nowadays, although poultry products are not the major source of human salmonellosis, they constitute a potentially hazardous source (Mataragas, Skandamis, & Drosinos, 2008). It is especially remarkable the case of products containing a high fat level and low water activity like peanut butter or chocolate (Podolak, Enache, Stone, Black, & Elliott, 2010). In these products the infective dose is low; i.e. a dose of 0.005 CFU/g in chocolate was found associated with an outbreak in Canada (Komitopoulou & Penaloza, 2009). For all exposed, *Salmonella* represents a major economic and welfare problem and therefore measures may be taken by all sectors of the food industry at all stages of the food chain, to minimize the incidence and level of this microorganism.

2. *Salmonella* in humans and animal species

The nature and severity of *Salmonella* infections in different animal species vary enormously and are influenced by many factors including the *Salmonella* serovar involved, strain virulence, infective dose, host animal species, age and immune status of the host, and the geographical region (Mastroeni & Maskell, 2006). The majority of salmonellosis cases in humans and domestic animals are caused by only relatively few serovars which can be subdivided into three groups on the basis of their host prevalence: serovars with a broad host range that usually cause subclinical intestinal infections or acute enteritis; and serovars for restricted or specific hosts that are associated with severe systemic diseases. The host specific serovars are less capable of inducing intestinal inflammatory responses. This could facilitate immune evasion and systemic spread through tissues. This pathogen property may be achieved either passively by loss of effector proteins involved in eliciting pro inflammatory responses, or actively through the evolutionary acquisition of effector proteins involved in the immune suppression. *Salmonella* can disseminate between animals principally through the feces, resulting in high levels of transmission and disease. High costs are spent annually by farming industries and public health services in monitoring and trying to control these pathogens. Knowledge of the pathogenesis of *Salmonella* infections in different animal species would help to find measures to stop this spread between animals (Mastroeni & Maskell, 2006).

3. Probiotics

Because at the present *Salmonella* is still a common pathogen in the industrial and developing countries and due to the undesired consequences of antibiotic treatments, scientists have been searching for alternative methods to control enteric infections. Probiotics appear as an attractive possibility to attend this concern. Probiotics are live microorganisms, which when administered in adequate amounts confer a health benefit on the host (FAO/WHO, 2001). The FAO/WHO specifically focused on probiotics as food or dietary supplements, but they also may be used in drug applications (as live biotherapeutics), microbial feed supplements (animal uses), genetically modified organisms, and live vaccines if administered orally. In an intent to enhance precision for probiotic definition, the International Scientific Association for Probiotics and Prebiotics (ISAPP, 2002) provided more detailed insight into the correct use of this term. The key aspects of this definition include the conditions for probiotics use in foods or in drugs. In the case of foods, probiotic strain/s used must be GRAS (Generally Regarded as Safe); must be a taxonomically defined microbe or combination of microbes (genus, species and strain level); must be alive when administered and have undergone controlled evaluation to document health benefits of the end products in the target host.

A probiotic used as a drug (non food use) must fulfill the general conditions stipulated above and moreover obey the rules of existing national regulations (i.e., US Food, Drug, and Cosmetic Act and EU Directive 2004/27/EC on substances used for treating or preventing disease) and guidelines on good clinical practices.

Some beneficial properties attributed to probiotic supplementation besides resistance to infectious disease are, for farm animals: improved growth rate, utilization of food, milk or egg production (Gaggia, Mattarelli, & Biavati, 2010; Lehloenya et al., 2008). For humans, they include at the gastrointestinal level, cancer prevention, regulation of peristalsis and decrease in the symptoms of lactose deficiency, prevention of antibiotic associated diarrhea, decrease of the gut inflammatory response and in the prevention of food allergy and gastrointestinal infections (de Vrese et al., 2001; Doron, Hibberd, & Gorbach, 2008; Kato, 2000; Marteau, de Vrese, Cellier, & Schrezenmeir, 2001; Miele et al., 2009; Vanderhoof, 2008).

4. Probiotics against salmonellosis

In the literature there are several clinical evidences that probiotics could be effective in the prevention and/or treatment of diarrheal diseases (Canani et al., 2007; Gill, 2003; Henker et al., 2007; McFarland, 2006).

The suggested mechanism by which probiotics might exert their protective or therapeutic effect against enteric pathogens include non immune mechanisms, such as the stabilization of the gut mucosal barrier, increasing the secretion of mucus, improving gut motility, and therefore interfering with their ability to colonize and infect the mucosa; competing for nutrients; secreting specific low molecular weight antimicrobial substances (bacteriocins) (Delgado, O'Sullivan, Fitzgerald, & Mayo, 2007; Liu et al., 2011), and influencing the composition and activity of the gut microbiota (regulation of intestinal microbial homeostasis). Table 1 summarizes the effects of probiotic strains on non immunological defenses.

Probiotics also exert their effect as immune adjuvants modulating the mucosal and systemic immune responses (Table 2). They can modulate the inflammatory response, stimulate certain cytokine production and phagocytic activity of macrophages and neutrophils, regulate NK cell activity, and enhance specific antibody responses, especially mucosal secretory IgA (Alvarez-Olmos & Oberhelman, 2001; Galdeano, de Moreno de LeBlanc, Vinderola, Bonet, & Perdigón, 2007; Gobbato et al., 2008; O'Hara et al., 2006).

4.1. Non immune mechanisms induced by probiotics (Table 1)

4.1.1. Stabilization of the gut mucosal barrier

In the gastrointestinal tract of humans and animals, mucosal barrier separates the internal milieu from the luminal environment. The local protection of mucosal surfaces is mediated by epithelial secretion products such as mucus, antimicrobial peptides (defensins) and secretory antibodies, mainly S-IgA. Mucus is composed by glycoproteins which are synthesized and secreted by goblet cells in response to physiological (indigenous microbiota) or pathological

Table 1
Effect of probiotics on non-immunological defenses against *Salmonella*.

Probiotic strain	Mechanism	Reference
• *L. plantarum* 299v and *L. rhamnosus* GG	Increase mucus secretion	Mack et al. (1999)
• *L. casei* CRL 431	Increase the number of goblet cells	Gauffin Cano et al. (2002b)
• Yogurt (*St. thermophilus* + *L. delbrueckii* ssp *bulgaricus*)		Gauffin Cano et al. (2002a)
• Fermented milk containing *L. casei* DN-114001		(de Moreno de LeBlanc, Dogi, et al., 2008)
		Maldonado Galdeano et al. (2009)
• *L. casei* CRL 431	Reinforce intestinal barrier integrity	Gauffin Cano et al. (2002b)
• *B. infantis*		Ewaschuk et al. (2008)
• VSL#3 (probiotic product consisting of *B. longum*, *B. infantis*, *B. breve*, *L. acidophilus*, *L. casei*, *L. bulgaricus*, *L. plantarum* and *St. salivarius* ssp *thermophilus*)		Madsen et al. (2001)
• Yogurt (*St. thermophilus* + *L. delbrueckii* ssp *bulgaricus*)		Gauffin Cano et al. (2002a)
• Fermented milk containing *L. casei* DN-114001	Increase bifidobacteria and decrease enterobacteria population in large intestine (in vivo)	de Moreno de LeBlanc, Dogi, et al. (2008)
• *B. breve* 4, *B. infantis* 1	Inhibit pathogen adhesion/ invasion (in vitro)	Bernet et al. (1993)
• *L. rhamnosus* GG + *L. casei* Shirota		Lee et al. (2003)
• *L. rhamnosus* GG alone		Burkholder and Bhunia (2009)
• *L. kefir*		Golowczyc et al. (2007)
• *L. gasseri* F71, *L. gasseri* L1, *L. paracassei* BA3, *L. paracassei* F76		Delgado et al. (2007)
• *B. lactis* Bb12 + *L. rhamnosus* GG		Collado et al. (2007)
• *L. plantarum* ACADC287		Fayol-Messaoudi et al. (2007)
• *L. acidophilus* LAP5		Lin et al. (2008)
• *L. gasseri* F71, *L. gasseri* L1, *L. paracassei* BA3, *L. paracassei* F76	Release antimicrobial substances	Delgado et al. (2007)
• *E. faecium* LM-2		Liu et al. (2011)
• *L. plantarum* ACA-DC287		Fayol-Messaoudi et al. (2007)
• *L. acidophilus* LAP5		Lin et al. (2008)
• *L. rhamnosus* GG		De Keersmaecker et al. (2006), Marianelli et al. (2010)

(enteric pathogens) stimuli. It protects the epithelium from direct contact with the luminal contents, acting as a barrier to avoid the invasion by pathogenic organisms. It forms a diffusion barrier that concentrates antimicrobial proteins near the epithelial cell surface increasing their effectiveness. Additionally, the formation of complexes between microbes and antibodies in the mucus cover layer, together with peristalsis, result in a rapid removal of this complexes from the small intestine trough feces (Hooper & Macpherson, 2010).

Several reports showed that probiotics induce in vivo or in vitro increased secretion of mucus (Macfarlane & Cummings, 2002; Mack et al., 1999). In this sense, it was demonstrated that *Lactobacillus casei* CRL 431 or yogurt administered as a supplement of the re nutrition diet in a malnutrition model in mice, efficiently improved the intestinal barrier and the mucosal immune system by increasing the number of goblet cells, S-IgA antibodies and IgA+ cells. This effect was also related with the protection observed in these animals when they were challenged with enteropathogenic bacteria (Gauffin Cano & Perdigón, 2003; Gauffin Cano et al., 2002a; 2002b). Other studies revealed that probiotic fermented milk administered to mice (newborns and adults) increased the number of goblet cells in the small intestine (de Moreno de LeBlanc, Dogi et al., 2008; Maldonado Galdeano et al., 2009), and this effect could be also related with the protection observed in these animals against *S.* Typhimurium infection (de Moreno de LeBlanc et al., 2011).

Intestinal permeability is another measure of gastrointestinal barrier function. Altered intestinal permeability due to enteropathogens and their toxins induces an abnormal transfer of antigens across the gut epithelium, triggering inflammation. It has been shown that probiotics induce factors that are able to reinforce intestinal barrier integrity and protect against pathogenic bacteria (Madsen et al., 2001).

4.1.2. Competition for adhesion

The first step in *Salmonella* pathogenesis is the adhesion/invasion to specific intestinal epithelial cells, principally in the ileum. It has been widely reported that adhesion of lactic acid bacteria to mucosa eliminates pathogen adhesion or the co culture of probiotic and pathogenic microorganisms decreases the adhesion of the pathogens using an in vitro system (Lee et al., 2003). *L. rhamnosus* GG reduced the adhesion and cytotoxicity of *Salmonella enterica* serovar Typhimurium during epithelial cell stress in vitro (Burkholder & Bhunia, 2009). *Lactobacillus* strains isolated from kefir grains were analyzed in vitro for their ability to interfere in the *Salmonella enterica* serovar Enteritidis interaction with epithelial cells. Co incubation of *Salmonella* with co aggregating strains significantly decreased its capacity to adhere to and to invade Caco-2/TC-7 cells. The authors also suggested a protective role of the S-layer protein from *L. kefir* involved in this effect (Golowczyc et al., 2007). Bernet et al. reported a dose dependent inhibition of adherence of *S.* Typhimurium to CaCO-2 cells by bifidobacteria in vitro (Bernet et al., 1993). It was demonstrated that four different *Lactobacillus* selected strains inhibited several *Salmonella* in an agar spot test, adhered to human Caco-2 and HT-29 epithelial cells, and also were unable to degrade pig gastric mucus in a plate assay (Delgado et al., 2007).

Other study suggests that certain combinations of probiotic strains inhibit the adhesion of different pathogens and the effect of the different combinations depended also in the pathogen used in each assay (Collado, Grzeskowiak, & Salminen, 2007; Collado, Meriluoto, & Salminen, 2007). The studies about the interference of probiotics with pathogen adhesion are performed using in vitro analysis but the in vivo conditions in the gastrointestinal tract should be considered. Therefore, further analyses to confirm adhesion inhibiting effects of probiotics in the intestine are necessary.

4.1.3. Secretion of antimicrobial substances

Several probiotic strains are able to produce a wide variety of antimicrobial substances. The most common are organic acids (lactic acid and acetic acid) which induce a reduction in fecal pH (Wohlgemuth, Loh, & Blaut, 2010), hydrogen peroxide, carbon dioxide, and antibacterial compounds, including bacteriocins and non bacteriocins, non lactic acid molecules (Fayol-Messaoudi, Berger, Coconnier-Polter, Lievin-Le Moal, & Servin, 2005; Marianelli et al., 2010). Six *Lactobacillus* strains including probiotic ones were

Table 2
Study of the immune mechanisms involved in the protective effect excerted by several probiotic strains against *Salmonella* infection in different host species. In vivo, ex vivo and in vitro assays.

Probiotic	Mechanism	Reference
Probiotic bacteria suspension		
• *L. casei* CRL 431	• Increases total and specific ati-*Salmonella* S-IgA • Increases IgA+ cells • Increases Bcl-2+ cells • Enhances phagocytic activity of macrophages • Increases IFN-γ, IL-10 and IL-4 levels • Modulates CD3, CD4 and CD8 population • Interacts with IECs through TLR2 inducing IL-6 production necessary for B-cell differentiation into plasma cells	(de Moreno de LeBlanc et al., 2010; Gauffin Cano et al., 2002b; Gauffin Cano & Perdigón, 2003; Gobbato et al., 2008; Perdigón et al., 1993; Vinderola et al., 2005)
• *L. delbrueckii ssp. bulgaricus* CRL 423	• Increases total S-IgA • Enhances microbicidal activity of macrophages • Inhibits cellular apoptosis • Increases Bcl-2+ cells • Increases IFN-γ levels	(Gobbato et al., 2008; Perdigón, Alvarez, et al., 1990; Valdez et al., 2001)
• *St. thermophilus* CRL 412	• Increases Total S-IgA antibodies • Enhances microbicidal activity of macrophages • Low inhibition of cellular apoptosis	(Gobbato et al., 2008; Perdigón, Alvarez, N.de Macías, et al., 1990; Valdez et al., 2001)
• *L. plantarum* 10hk2	• Increases the secretion of IL-1β, IL-6 and TNF-α, as well as IL-10 by RAW cells	Chon and Choi (2010)
• Multi-strain probiotic mix	• Increases IgA and IgG	Mountzouris et al. (2009)
• *B. longum* Bb46	• Reduces inflammatory response	Silva et al. (2004)
• *B. animalis subsp. lactis* (Bifido B)	• Increases S-IgA and IL-10 • Antagonism in vitro (non-immune mechanism)	Martins, Martins, et al. (2011)
• *Saccharomyces cerevisiae* UFMG 905	• Decreases levels of proinflammatory cytokines • Modulates the activation of mitogen-activated protein kinases (p38 and JNK, but not ERK1/2) • Modulates NF-κB and AP-1, involved in activation of proinflammatory mediators	Martins, Elian, et al. (2011)
• *L. helveticus* R389	• Interacts with IECs inducing IL-6 production, necessary for B-cell differentiation into plasma cells	Vinderola et al. (2005)
• *B. infantis* 35624	• Modulates the epithelium by inhibiting the constitutive secretion of IL-8 and attenuating *S.* Typhimurium-induced NF-κB activation and IL-8 secretion	O'Hara et al. (2006)
• *L. salivarius* UCC118	• Stimulates the secretion of IL-10 and TNF-α by myeloid DCs.	
• *L. acidophilus* CRL 730	• Increases total S-IgA antibodies	(de Moreno de LeBlanc, Dogi, et al., 2008; Gauffin Cano et al., 2002b; Perdigón et al., 1993; Perdigón, Alvarez, et al., 1990)
• *L. rhamnosus* HN001	• Increases titers of serum and intestinal tract anti-*Salmonella* antibodies	Gill et al. (2001)
• *B. lactis*	• Increases splenic lymphocyte proliferative responses to mitogens • Increases blood and peritoneal cell phagocytic activity • Enhances anti-*S.* Typhimurium antibody titers in intestinal mucosa	Shu et al. (2000)
Fermented milks containing probiotic bacteria		
• Probiotic dahi (with *L. casei*)	• Increases S-IgA levels • Increases lymphocyte proliferation rate • Augmented IL-2, IL-6, and IFN-γ and diminished IL-4 production by cultured splenic lymphocytes	Jain et al. (2009)
• Probiotic dahi (curd) with *L. acidophilus* and *L. casei*	• Increases anti-*S.* Enteritidis S-IgA • Increases lymphocyte proliferation • Increases IL-2, IL-6 and IFN-γ production in supernatant of cultured splenocytes	Jain et al. (2008)
• *L. casei* CRL 431+ *L. acidophilus* CRL 730	• Stimulate specific anti *Salmonella* S-IgA	Perdigón, N.de Macías, et al. (1990)
• *L. helveticus* R389 or its non bacterial fraction	• Diminish the number of MIP-1α+ cells in the lamina propria of small intestine • Induce IL-6 secretion by IEC necessary for B-cell differentiation into plasma cells • Augment total and specific anti *Salmonella* S-IgA • Increment IgA+ cells in the lamina propria of small intestine	Vinderola et al. (2007)
• *L. casei* DN-114001 (administered to adult mice)	• Increases total S-IgA antibodies • Increases IgA+ cells in the lamina propria of small intestine • Increases CD4 and CD8+ cells • Increases the number of macrophages (F4/80+ cells) in the lamina propria of small intestine • increases the number of calcineurin+ cells in the LP • Induces IL-6 secretion by IEC • Increases dendritic cell populations • Increases MIP-1α+ cells in the lamina propria of small intestine • Increases microbicidal activity • increases CD206+ cells • Modulates TLR-4 expression	(de Moreno de LeBlanc, Dogi, et al., 2008; Maldonado Galdeano et al., 2009)
• *Lactobacillus acidophilus* La1 + *Bifidobacterium bifidum* Bb12	• Increases anti *Salmonella* Typhi antibody response • Increases serum total IgA level	Link-Amster et al. (1994)

analyzed for their capacity to inhibit *S.* Typhimurium SL1344 invasion into cultured Caco-2/TC7 cells. The antibacterial activity of some of them was solely due to the production of lactic acid, but for other strains was due to the production of lactic acid and another unknown inhibitory substance(s) (Makras et al., 2006). Another in vitro study showed that the antimicrobial activity of *L. rhamnosus* GG against *S.* Typhimurium was due to accumulation of lactic acid (De Keersmaecker et al., 2006). Fayol-Messaoudi et al. investigated

the antibacterial activity *L. plantarum* ACA-DC287 isolated from a Greek cheese, and determined that the co culture of *L. plantarum* strain with *S.* Typhimurium resulted in the killing of the pathogen due to non lactic acid molecules that were present in the cell free culture supernatant of this probiotic strain (Fayol-Messaoudi et al., 2007). The culture of the *L. plantarum* also inhibited the penetration of *S.* Typhimurium into cultured human enterocyte like Caco-2/TC7 cells. Lin et al. reported a probiotic strain able to inhibit the invasion of *Salmonella* Choleraesuis to human Caco-2 cell line in vitro by multiple mechanisms, including the production of organic acids and bacteriocins (Lin et al., 2008).

Bacteriocins produced by lactic acid bacteria (LAB) had been well characterized (Castro, Palavecino, Herman, Garro, & Campos, 2011; Cintas et al., 2000) and there are many reports where bacteriocins produced by probiotic LAB contribute to the health of the gastrointestinal tract (Gillor, Etzion, & Riley, 2008). However, the probiotic applications of bacteriocins produced by Gram positive bacteria on the gastrointestinal tract are limited because they rarely inhibit commonly encountered enteropathogenic bacteria such as *Salmonella*, *Enterobacter*, or *Klebsiella*.

4.2. Immune mechanisms stimulated by probiotics (Table 2)

4.2.1. Effect of probiotic bacteria suspension

The protective effects exerted by probiotic suspensions against different *Salmonella* serovars, are well documented. Mountzouris et al. reported that an orally delivered probiotic (multi strain) reduced *S.* Enteritidis levels in broilers (Mountzouris et al., 2009). They observed that probiotic feeding significantly increased IgA and IgG antibodies against *S.* Enterica at systemic and at intestinal level, and reduced the incidence of infected animals in treated groups (50%) compared with untreated controls (100%). Other probiotic strains, *L. rhamnosus* HN001 and *B. lactis* HN019 showed to have protective properties against *S.* Typhimurium in mice, by increasing specific anti *Salmonella* antibodies in serum and intestinal tract, increasing splenocyte proliferative responses to mitogens, and phagocytic activity of peritoneal and blood cells (Gill et al., 2001; Shu et al., 2000). The importance of the lactobacillus S-layer protein in the immune protection was also reported using mice infected with *S.* Typhimurium and administered with the probiotic strain *L. helveticus* M92. The authors suggested that the reduced infection by *S.* Typhimurium FP1 was associated with competitive exclusion in the intestinal tract of the mice and enhanced immune protection conferred by the *L. helveticus* M92 and its S-layer protein. (Beganovic et al., 2011)

The anti-inflammatory effect of certain probiotic bacteria could be also related with the protection of these microorganisms against pathogens. Host defense against infection activates the inflammatory immune response that may lead to tissue damage (Fig. 1). In this sense, another study demonstrated the anti-inflammatory and pathogen protection benefits of *Bifidobacterium infantis* 35624, a probiotic bacterial strain of human origin, administered to mice previous to the infection with *Salmonella typhimurium* or the injection with LPS. The beneficial effect of this probiotic was related to the induction of Treg cells which controlled the excessive NF-κB activation in vivo (O'Mahony et al., 2008) (Fig. 2).

Research conducted in our laboratory demonstrated that the oral administration of *L. casei* CRL 431, *L. acidophilus* CRL 730, *L. delbrueckii* subsp. *bulgaricus* CRL 423 and *Streptococcus* (*St.*) *thermophilus* CRL 412 to healthy BALB/c mice increased the total S-IgA measured in the intestinal fluid (Perdigón, Alvarez, N.de Macías, & P.de Ruiz Holgado,

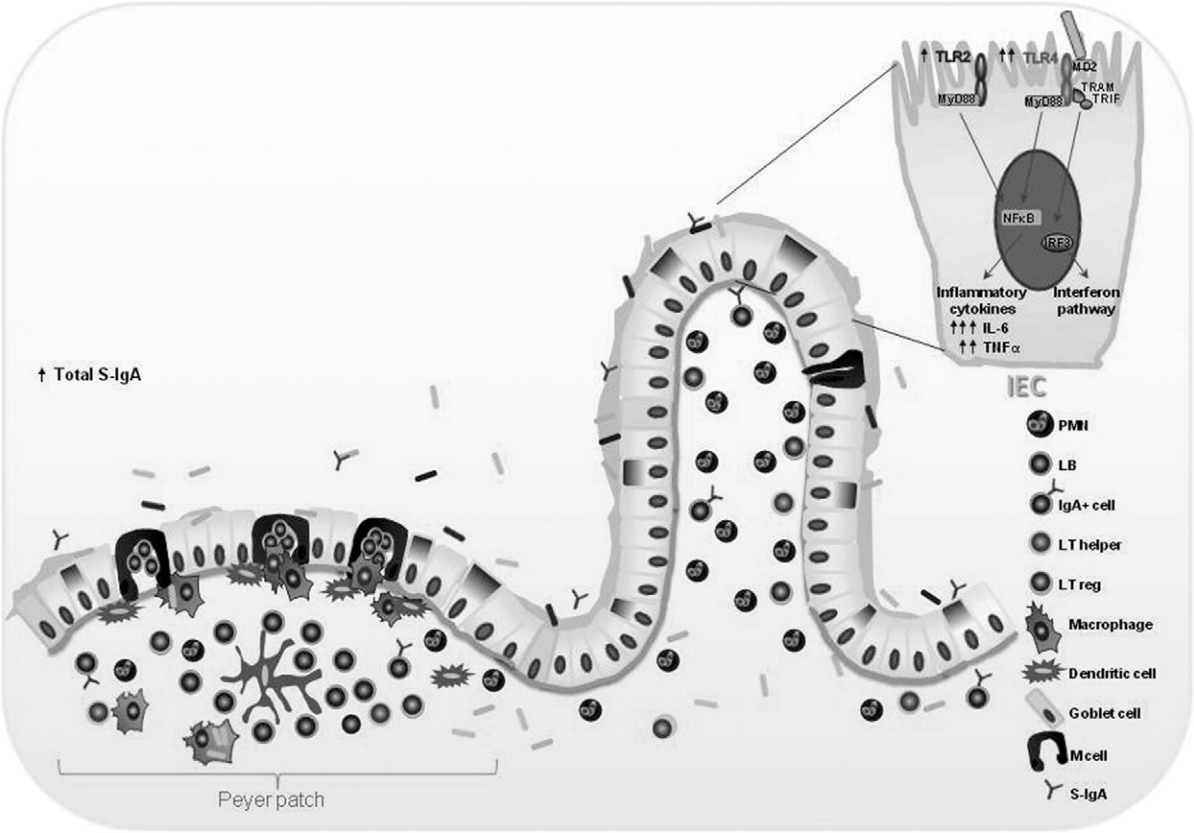

Fig. 1. Scheme of the immune mechanisms induced against *Salmonella* infection in the inductor (Peyer's patches) and effector (lamina propria and epithelium) sites of the gut immune response. *Salmonella* enters through M cells or intestinal epithelial cells (IECs), then internalizes and replicates within phagocytic cells, and induces their cellular death, mechanism used to disseminate to deeper tissues. The infection generally induces an inflammatory response with infiltration of polymorphonuclear cells, and the activation of inflammatory cascades into the epithelial and immune cells to produce pro-inflammatory cytokines and severe tissue damages.

1990; Perdigón et al., 1993). The LAB assayed were also able to induce a significant increase in the number of IgA secreting cells associated with the gut and the effect was dependent of the feeding period (Perdigón, Maldonado Galdeano, Valdez, & Medici, 2002). It was also reported that all these LAB strains induced a different profile of the cytokine positive cells such as TNF-α, IFN-γ, IL-12, IL-6, IL-2, IL-4 and IL-10. Even though all the strains assayed induced pro-inflammatory cytokines consequently we observed a high number of IL-10 and IL-4 regulatory cytokines (Maldonado Galdeano & Perdigon, 2004). The impact of probiotics on the intestinal epithelial cells was also reported (Vinderola et al., 2005).

This knowledge led us to study the effect of these LAB administrations to well nourished mice, against enteric infection caused by *S.* Typhimurium. We have also performed in vitro and ex vivo studies to elucidate the mechanisms involved in the preventive capacity of the strains assayed (Perdigón, Alvarez, & P.de Ruiz Holgado, 1991). It was observed an increased resistance against *S.* Typhimurium in the mice given *L. casei, L. delbrueckii* subsp. *bulgaricus* and *St. thermophilus* but not *L. acidophilus*. The specific anti pathogen S-IgA was increased for *L. casei* but not for *L. delbrueckii* subsp. *bulgaricus* and *St. thermophilus.* This protective effect was dose dependent and it was remarkable for *L. casei* against *Salmonella* (Perdigón, Alvarez, Gobbato, de Budeguer, & de Ruiz Holgado, 1995). The specific S-IgA found would be one of the mechanisms to affording protection against the pathogen assayed because neutralizes the pathogen and prevents pathogen internalization in the gut (Fig. 2).

Other mechanisms implicated in the protection against *Salmonella* afforded by the LAB such as *L. delbrueckii* subsp. *bulgaricus* and *St. thermophilus* were analyzed. Valdez et al. performed an in vitro assay using peritoneal macrophages obtained from BALB/c mice, and determined that these LAB were able to stimulate the release of oxidant radicals such as superoxide and hydrogen peroxide, and to inhibit the *S.* Typhimurium induced apoptosis in the macrophages (Valdez et al., 2001). This is relevant because *Salmonella* internalizes and replicates within the phagocytic cells, and then induces their apoptosis or pyroptosis. These mechanisms are used for the dissemination to other tissues, so these last processes are an important step in the pathogenesis of *Salmonella* infection (Mastroeni, Grant, Restif, & Maskell, 2009; Mastroeni & Maskell, 2006; Wallis & Galyov, 2000). In the same work, it was demonstrated that *L. casei* CRL 431 also stimulated the release of oxidants radicals, but was not capable to induce an inhibition of the cellular apoptosis of the in vitro infected peritoneal macrophages (Valdez et al., 2001).

Gobbato et al. evaluated the same LAB in the protection against *S.* Typhimurium in vivo, using a mouse model (Gobbato et al., 2008). They reported a significant decrease in the number of apoptotic cells in the small intestine tissues, especially in mice fed with *L. bulgaricus*. This result could be explained by the important increase in the number of anti apoptotic protein Bcl-2+ cells found in the small intestine of the mice that received this LAB. *St. thermophilus* did not induce an increase in the number of Bcl-2+ cells compared to the untreated control and did not exert effect on apoptosis inhibition. Instead, *L. casei* administration increased the number of Bcl-2+ cells, but its effect on the apoptosis inhibition was similar to *St. thermophilus*. The increase in the number of IFNγ+ cells in the small intestine of mice given *L. delbrueckii* subsp. bulgaricus was also observed. This fact was consistent with the increased microbicidal activity observed in the macrophages isolated from peritoneum and Peyer's patches after this LAB oral administration. *L. casei* also increased the number of IFNγ+ cells, but this increase was not enough to induce the microbicidal activity of the peritoneal macrophages. This *Lactobacillus* also causes increases in other regulatory cytokines, such as IL-4 and

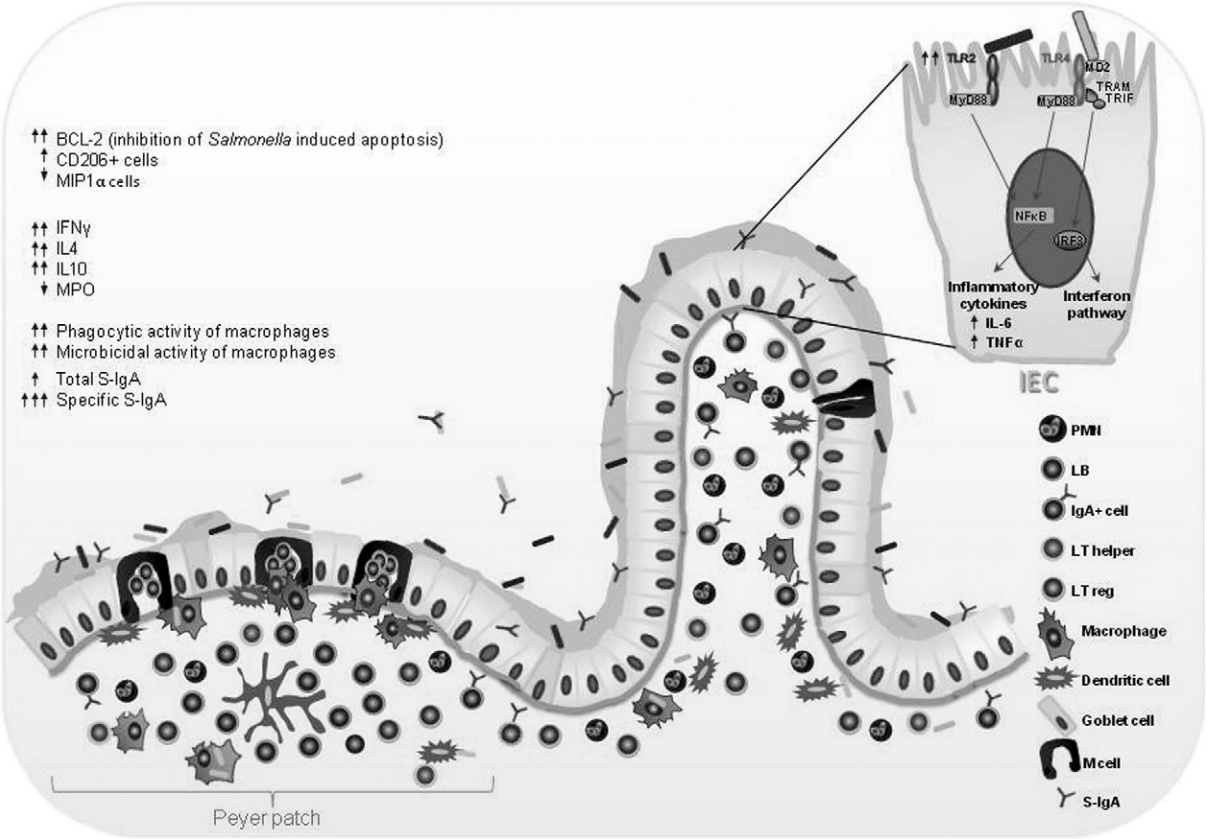

Fig. 2. Scheme of some immune mechanisms induced by different probiotic strains against *Salmonella* infection. Probiotics induce an anti-inflammatory response with increase of Treg cells, macrophages and dentritic cells that produce regulatory cytokines such as IL-10. Probiotics also increase mucus producer cells and IgA-secreting cells that reinforce the intestinal defenses.

IL-10, that could modulate the effect of IFNγ (Perdigón et al., 2002). *St. thermophilus* exerted a partial protective effect by apoptosis inhibition and by the increased microbicidal activity.

The importance of the LAB viability to exert the protection against *Salmonella* infection was also analyzed. It was demonstrated that viable *L. casei* rather than non viable lactobacilli prevented *Salmonella* infection with high levels of pathogen specific S-IgA. (Alvarez, Gobbato, Bru, P.de Ruiz Holgado, & Perdigón, 1998). Recently, the importance of the continuous probiotic *L. casei* CRL 431 administration before and after infection was evaluated in vivo using a mouse model. Although oral administration before infection decreased the severity of the infection with *S.* Typhimurium, it was demonstrated that the continuous administration (even after infection) had the best effect (de Moreno de LeBlanc et al., 2010). This continuous administration diminished the counts of the pathogen in the large intestine as well as their spread outside this organ. H-E staining of histological slices from small intestine revealed decreased number of polymorphonuclear cells (PMN), accompanied with increased number of mononuclear cells in the lamina propria of the small intestine obtained from mice administered probiotics, compared to the infected controls. *L. casei* acted on cells of the innate and adaptive immune response, decreasing the PMN infiltration with the consequent diminution of intestinal inflammation (which was assessed by myeloperoxidase levels), increased the phagocytic activity of macrophage isolated from different sites such as Peyer's patches, spleen and peritoneum, and increased the number of IgA+ cells in the lamina propria of the small intestine which was correlated with an increased release of anti pathogen specific S-IgA in the intestinal fluids (Fig. 2). However, *L. casei* CRL 431 was not able to inhibit the cellular death induced by *Salmonella*, revealing that this mechanism was not the way by which the probiotic exerted its protective effect (de Moreno de LeBlanc et al., 2010).

Besides the studies performed in well nourished mice, it is important to consider the administration of probiotic microorganisms in immune compromised hosts. Nutritional deficiency is commonly associated with impaired immune response; therefore the relation between infection and malnutrition is synergic. The safety of *L. casei* CRL 431 administration in malnourished mice was described (Gauffin Cano et al., 2002b). The authors showed that given probiotic as re nutrition diet recovered the gut barrier and mucosal immune function. Based in these observations, the supplementation with probiotic bacteria was used as adjuvants in a re nutrition diet in a non severe malnutrition mouse model to analyze their possible protective effect against *S.* Typhimurium infection. *L. casei* suspension added to the re nutrition diet increased the release of anti *Salmonella* S-IgA to the intestinal lumen and the number of IgA+ cells in the lamina propria of the small intestine. It was also reported that when these mice were infected with *S.* Typhimurium, *L. casei* administration prevented the infection after 14 days of re nutrition. This protection was mediated by increased specific S-IgA secretion into the intestinal fluid and increased number of IgA+ cells (Gauffin Cano & Perdigón, 2003).

4.2.2. Effect of fermented milk contained LAB

The administration of a mix of *L. casei* CRL 431 and *L. acidophilus* CRL 730 in fermented and non fermented milk was evaluated using a model of *S.* Typhimurium infection in BALB/c mice. The results showed that the fermented mixture was more effective than the non fermented one in the increased resistance against *Salmonella*. High levels of specific S-IgA were also found in the mice that received the fermented milk (Perdigón, N.de Macías, Alvarez, Oliver, & P. de Ruiz Holgado, 1990).

Several studies provide strong evidences for the hypothesis that yogurt consumption may enhance immunity (Perdigón, Alvarez, de Macías, et al., 1991; Perdigón, Alvarez, N.de Macías, & Medici, 1989; Perdigón, Rachid, De Budeguer, & Valdez, 1994). According to these previous results, different doses of yogurt were given to mice as re nutrition diet supplement and its effects against *S.* Typhimurium infection were evaluated in a malnutrition model. It was demonstrated that in malnourished and non infected mice, yogurt was beneficial to improve nutritional and immunological parameters, giving better recovery of intestinal function than the re nutrition with milk (Gauffin Cano et al., 2002a). However, yogurt administration did not exert the same protective effect reported for *L. casei* CRL 431 administration using the same murine model of malnutrition and infection (Gauffin Cano & Perdigón, 2003). This comparative study showed that even when immunomodulatory properties are reported for a probiotic product or a bacterial strain, the effect against a pathogenic agent depends of the specific pathogen and probiotic strain assayed.

The importance of the non bacterial fraction and the products released during milk fermentation by LAB in the immunomodulatory effects of the fermented milks was reported (LeBlanc, Matar, Valdez, LeBlanc, & Perdigon, 2002; Vinderola, Perdigón, Duarte, Farnworth, & Matar, 2006). The participation of the bacterial free fraction obtained from milk fermented with *L. helveticus* R389 in the protection of mice against *S.* Typhimurium infection was also analyzed. Both milk fermented by *L. helveticus* R389 and its non bacterial fraction were able to enhance protection against *S.* Typhimurium infection in vivo (Vinderola et al., 2007). Both products administered to BALB/c mice decreased the spread of the pathogen to the liver with high percentages of mouse survival after the infection, low numbers of MIP-1α+ cells in the lamina propria (inflammation marker) and high luminal concentration of total and specific anti *Salmonella* S-IgA, accompanied with an increased number of IgA+ cells in the lamina propria of the small intestine. The authors showed some differences between fermented milk and its bacterial free supernatant related to the production of specific S-IgA and the number of MIP-1α producing cells. They hypothesized that after fermentation at controlled pH 6, there was an increase in the content of bioactive peptides and other bioactive molecules in the non bacterial fraction (Vinderola et al., 2006) and this fact might be the reason for the better protection that this product provided against the infection (Vinderola et al., 2007).

There are many reports about the beneficial effect of the consumption of fermented milk containing the probiotic strain *L. casei* DN-114001 (de Moreno de LeBlanc, Dogi, et al., 2008; Maldonado Galdeano et al., 2009; Medici, Vinderola, Weill, & Perdigon, 2005; Meyer, Elmadfa, Herbacek, & Micksche, 2007). It was observed that long term administration of fermented milk containing the probiotic bacterium *L. casei* DN-114001 had immunomodulatory properties and maintained the intestinal homeostasis without adverse secondary effects in mice (de Moreno de LeBlanc, Chaves, et al., 2008). This probiotic fermented milk (PFM) was evaluated in the protection against *S.* Typhimurium when this product was administered to mice continuously before and after infection or only post infection (de Moreno de LeBlanc et al., 2011). The results showed that PFM administration after *Salmonella* infection decreased the severity of the infection, but the best effect was obtained with continuous PFM administration. The study of possible cell receptors and populations involved in the immune activation induced by *S.* Typhimurium and/or by the probiotic fermented milk showed that PFM administration increased the number of IgA+ cells and CD206+ cells in the lamina propria of the small intestine. This observation agrees with other reports where the oral administration of the probiotic strain *L. casei* CRL 431 to healthy mice increased this receptor in the immune cells of the innate immune response in both lamina propria and Peyer's patches of the small intestine (Galdeano & Perdigon, 2006). Another receptor analyzed was TLR4 because it recognizes the LPS present in the membrane of the Gram-negative bacteria, such as *Salmonella* and it is know that this receptor is required to control *Salmonella* infection. PFM maintained increased the number of TLR4+ cells before the infection, but after *Salmonella* challenge the number of TLR4+ cells decreased in all the groups

compared with the basal data, being these decreases more important for the mice fed with PFM, which could be related with the decrease in the severity of the infection for these groups. It is known that the activation of TLR4 initiates an innate immune response leading to the induction of pro inflammatory mediators but then leads to the suppression of its own mRNA expression during *Salmonella* infection (Totemeyer, Foster, Kaiser, Maskell, & Bryant, 2003).

It was also demonstrated that the administration of fermented milk containing the probiotic strain *L. casei* DN-114001 during nursing exerts beneficial impact on the mouse microbiota development of the offspring and this effect was related with a modulation of two important immune cell populations, macrophages and dendritic cells that are involved in both innate and acquired immunity (de Moreno de LeBlanc, Dogi, et al., 2008). Considering this previous report, the adjuvant effect if this PFM against *S.* Typhimurium infection in early period of the life was evaluated in newborn mice, from mothers that received the PFM during the suckling period or their offspring after weaning (de Moreno de LeBlanc et al., 2011). PFM was effective against *S.* Typhimurium infection when it was administered to the offspring after weaning or when their mother were given PFM during suckling period, showing the importance of the PFM administration in early period of the life to prevent *S.* Typhimurium infection.

Summarizing, previous results demonstrate that the principal mechanism involved in the protection against *Salmonella* is the enhancement of the innate immune response, through the activation of macrophages, and the receptors such as CD206+, TLR2 and TLR4 with greater infiltration of mononuclear than polymorphonuclear cells in the lamina propria of the small intestine. Probiotic strains are able to interact with intestinal epithelial cells, increasing TLR4 expression and cytokine secretion, turning these cells in the first sentinels against pathogen infection.

5. Probiotic effects in human health and against *Salmonella* infection: in vitro evidence and clinical trials

In vivo, ex vivo and in vitro assays performed in animal models significantly contributes to a better understanding of certain aspects of host bacteria interactions. They offer the possibility to use animals with a virtually identical genetic background (inbred strains) and to put them under the same feeding and housing conditions, factors that are highly variable in humans. Nevertheless, the physiology of animals differs considerably from that of humans, and therefore exist a little risk that they may fail in properly modeling a human subject. For this reason, probiotics for human use require validation of their efficacy through human clinical trials. Appropriate target specific in vitro tests that correlate with in vivo results should be also performed (i.e., a study of low pH resistance correlates with gastric survival in vivo). However, all of these tests require validation, with in vivo performance. In humans, probiotics can find their main application in the prevention of gastrointestinal diseases or disorders, more than in a curative approach. This is because the action of probiotics is not generally aimed as for antibiotics to kill pathogen bacteria; they modulate the gastrointestinal environment reducing the risk of gastrointestinal disease synergistically with the immune system of the host (Gaggia et al., 2010). Probiotic for human consumption in foods must be GRAS. This means that no adverse effects related to probiotic administration should be demonstrated. Most probiotic foods contain lactobacilli and/or bifidobacteria, mainly bacterial strains of members of the heterogeneous group of lactic acid bacteria; lactobacilli (*L. acidophilus, L. casei, L. plantarum, L. reuteri, L. rhamnosus*, and *L. salivarus*), bifidobacteria (*B. breve*, *B. longum*, and *B. lactis*), *Bacillus* (*B. subtilis,* and *B. cereus* var. *toyoi*) and *Enterococcus* (*E. faecium)* among others, and the yeast *S. cerevisiae* variety *boulardii* were also used to attenuate enteric infections (Binns & Lee, 2010; Maragkoudakis, Chingwaru, Gradisnik, Tsakalidou, & Cencic, 2010; Mumy Kl Fau - Chen, Chen X Fau - Kelly, Kelly Cp Fau - McCormick, & McCormick, 2008) . Although most of the probiotic species and genera are apparently safe, certain microorganisms, particularly the enterococci, could be problematic (Liu, Zhang, Dong, Yuan, & Guo, 2009). There is evidence they have emerged as opportunistic pathogens in hospital environments causing nosocomial infections and may also harbor transmissible antibiotic resistance determinants (i.e. vancomycin resistant *Enterococcus* strains) (Foulquie Moreno, Sarantinopoulos, Tsakalidou, & De Vuyst, 2006; Lee, Lee, & Lee, 2008; Watson & Preedy, 2010). Also bacilli, especially those belonging to the *B. cereus* group are known to produce enterotoxins and an emetic toxin (Duc le, Hong, Barbosa, Henriques, & Cutting, 2004).

As described previously, many in vitro studies using human cells to report probiotic protection against salmonellosis has been made. One alternative used to study the mechanisms exerted by probiotic in humans are the assays carried out in human microbiota associated (HMA) animals. Wagner et al. observed that the application of probiotic lactobacilli and bifidobacteria reversed a *Salmonella* induced immune suppression in immune competent HMA mice after experimental infection (Wagner, Johnson, & Kurniasih Rubin, 2009). Nevertheless, only little number of clinical trials on healthy volunteers has been reported. In example, Link-Amster, gave to 16 volunteers a fermented milk supplemented with *L. acidophilus*, *Bifidobacterium* Bb12 and *St. thermophilus* for 3 weeks, and in parallel they ingested attenuated *Salmonella* Typhi Ty21a vaccine. He found that the specific serum IgA titer rise was significantly higher in the test group than in controls, denoting an enhancement of the humoral immune response (Link-Amster et al., 1994). Similarly, it was reported that the oral consumption of *L. rhamnosus* GG and *Lactococcus lactis* simultaneously with an oral vaccine of attenuated *Salmonella* Typhi, increased specific IgA in the subjects receiving the vaccine in combination with *Lactobacillus* GG. Those receiving *Lactococcus lactis* with their vaccine augmented CR3 receptor expression on neutrophils compared with those receiving either the placebo or *Lactobacillus* GG (Fang, Elina, Heikki, & Seppo, 2000). In 2007, it was demonstrated that the oral consumption of a probiotic product containing *L. coryniformis* CECT5711 and *L. gasseri* CECT5714 improved intestinal microbiota of healthy children, enhancing the defense against gastrointestinal aggressions by reducing citotoxicity of fecal samples, and infections by inhibiting *Salmonella* Choleraesuis adhesion to intestinal mucins, and enhancing IgA concentration in feces and saliva (Lara-Villoslada, Sierra, Boza, Xaus, & Olivares, 2007). A significantly higher serum IgA antibody response to *Salmonella* Typhi in subjects given fermented milk containing *B. bifidum* and *L. acidophilus* La1 following vaccination with *Salmonella* Typhi Ty21 was also reported (Link-Amster et al., 1994). Similar observations for *Salmonella* specific IgA secreting cell responses was reported in volunteers given *Lactobacillus* GG and immunized with a *Salmonella* vaccine (Fang et al., 2000). The ability of some LAB strains to reduce the carrier state of *Salmonella* and *Shigella* in children with enteritis has also been reported (Pathmakanthan S, 2000).

6. Conclusion

Based in the extensive research exposed above, probiotics consumption may constitute a good alternative in the prevention and/or treatment of salmonellosis. We can hypothesize that in the treatment of non severe disease (when no antibiotic treatment is necessary) probiotics can ameliorate the clinical status of the host, by modulating the inflammatory response in the gut, diminishing mucosal damage and optimizing innate immune cellular response against this pathogen. In severe cases (Typhoid fever), where the antibiotic treatment is imperative, probiotic administration could be also recommended as a complement to reduce the risk of *Salmonella* dissemination to other organs (sepsis) and to diminish the secondary effects of antibiotic treatments as well as the time of administration of them.

There are several non immune and immune mechanisms by which a probiotic strain may confer protection against *Salmonella* infection,

and it is important to remark that these mechanisms are species and/or strain specific. There are also evidences that in some cases, a mix of probiotic strains can be more useful than each strain alone against this infection. In addition, the presence of one or more probiotic strains in a fermented product can improve the beneficial properties of the probiotic strains involved. We demonstrated the security of probiotics administration after *Salmonella* infection in healthy host and in immunosuppressed or babies hosts. Although, the major part of the researches were performed in animal models through in vivo assays or by in vitro studies using human cell lines, some studies carried out in humans to verify the probiotic effects were also addressed in the present review, therefore is of critical importance to perform more clinical trials in humans to validate the results obtained with each specific probiotic strain or probiotic products.

Acknowledgments

This work had been financially supported by Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET, PIP 0652), Consejo de Investigación de la Universidad Nacional de Tucumán (CIUNT 26/D442), and by a grant between DANONE S.A. and CONICET.

References

Alvarez, S., Gobbato, N., Bru, E., P.de Ruiz Holgado, A., & Perdigón, G. (1998). Specific immunity induction at mucosal level by viable *Lactobacillus casei*. Perspective for oral vaccine development. *Food Agricultural Immunology*, *10*, 79–87.

Alvarez-Olmos, M. I., & Oberhelman, R. A. (2001). Probiotic agents and infectious diseases: A modern perspective on a traditional therapy. *Clinical Infectious Diseases*, *32*(11), 1567–1576.

Arthur, L., Jones, S., Fabri, M., & Odumeru, J. (2007). Microbial survey of selected Ontario-grown fresh fruits and vegetables. *Journal of Food Protection*, *70*(12), 2864–2867.

Beganovic, J., Frece, J., Kos, B., Lebos Pavunc, A., Habjanic, K., & Suskovic, J. (2011). *Functionality of the S-layer protein from the probiotic strain Lactobacillus helveticus M92.* : Antonie Van Leeuwenhoek.

Bell, C., & Kyriakides, A. (2002). *Salmonella: A practical approach to the organism and its control in foods.* : Blackwell Science.

Bernet, M. F., Brassart, D., Neeser, J. R., & Servin, A. L. (1993). Adhesion of human bifidobacterial strains to cultured human intestinal epithelial cells and inhibition of enteropathogen–cell interactions. *Applied and Environmental Microbiology*, *59*(12), 4121–4128.

Binns, C., & Lee, M. K. (2010). The use of probiotics to prevent diarrhea in young children attending child care centers: A review. *Journal of Experimental & Clinical Medicine*, *2*(6), 269–273.

Burkholder, K. M., & Bhunia, A. K. (2009). *Salmonella enterica* serovar Typhimurium adhesion and cytotoxicity during epithelial cell stress is reduced by *Lactobacillus rhamnosus* GG. *Gut Pathogens*, *1*(1), 14.

Canani, R. B., Cirillo, P., Terrin, G., Cesarano, L., Spagnuolo, M. I., De Vincenzo, A., et al. (2007). Probiotics for treatment of acute diarrhoea in children: Randomised clinical trial of five different preparations. *BMJ*, *335*(7615), 340.

Castro, M. P., Palavecino, N. Z., Herman, C., Garro, O. A., & Campos, C. A. (2011). Lactic acid bacteria isolated from artisanal dry sausages: Characterization of antibacterial compounds and study of the factors affecting bacteriocin production. *Meat Science*, *87*(4), 321–329.

Chon, H., & Choi, B. (2010). The effects of a vegetable-derived probiotic lactic acid bacterium on the immune response. *Microbiology and Immunology*, *54*(4), 228–236.

Cintas, L. M., Casaus, P., Herranz, C., Havarstein, L. S., Holo, H., Hernandez, P. E., et al. (2000). Biochemical and genetic evidence that *Enterococcus faecium* L50 produces enterocins L50A and L50B, the sec-dependent enterocin P, and a novel bacteriocin secreted without an N-terminal extension termed enterocin Q. *Journal of Bacteriology*, *182*(23), 6806–6814.

Collado, M. C., Grzeskowiak, L., & Salminen, S. (2007a). Probiotic strains and their combination inhibit in vitro adhesion of pathogens to pig intestinal mucosa. *Current Microbiology*, *55*(3), 260–265.

Collado, M. C., Meriluoto, J., & Salminen, S. (2007b). Role of commercial probiotic strains against human pathogen adhesion to intestinal mucus. *Letters in Applied Microbiology*, *45*(4), 454–460.

De Keersmaecker, S. C., Verhoeven, T. L., Desair, J., Marchal, K., Vanderleyden, J., & Nagy, I. (2006). Strong antimicrobial activity of *Lactobacillus rhamnosus* GG against *Salmonella typhimurium* is due to accumulation of lactic acid. *FEMS Microbiology Letters*, *259*(1), 89–96.

de Moreno de LeBlanc, A., Chaves, S., Carmuega, E., Weill, R., Antoine, J., & Perdigón, G. (2008a). Effect of long-term continuous consumption of fermented milk containing probiotic bacteria on mucosal immunity and the activity of peritoneal macrophages. *Immunobiology*, *213*(2), 97–108.

de Moreno de LeBlanc, A., Dogi, C. A., Maldonado Galdeano, C., Carmuega, E., Weill, R., & Perdigón, G. (2008b). Effect of the administration of a fermented milk containing *Lactobacillus casei* DN-114001 on intestinal microbiota and gut associated immune cells of nursing mice and after weaning until immune maturity. *BMC Immunology*, *9*, 27.

de Moreno de LeBlanc, A., Castillo, N. A., & Perdigón, G. (2010). Anti-infective mechanisms induced by a probiotic Lactobacillus strain against *Salmonella enterica* serovar Typhimurium infection. *International Journal of Food Microbiology*, *138*(3), 223–231.

de Moreno de LeBlanc, A., Maldonado Galdeano, C., Dogi, C. A., Carmuega, E., Weill, R., & Perdigón, G. (2011). Adjuvant effect of a probiotic fermented milk in the protection against *Salmonella enteritidis* serovar Typhimurium infection: Mechanisms involved. *International Journal of Immunopathology and Pharmacology*, *23*(4), 1235–1244.

de Vrese, M., Stegelmann, A., Ritcher, B., Fenselau, S., Laue, C., & Schrezenmeir, J. (2001). Probiotics-compensation for lactase insufficiency. *The American Journal of Clinical Nutrition*, *73*, 421–429.

Delgado, S., O'Sullivan, E., Fitzgerald, G., & Mayo, B. (2007). Subtractive screening for probiotic properties of lactobacillus species from the human gastrointestinal tract in the search for new probiotics. *Journal of Food Science*, *72*(8), M310–M315.

Doron, S. I., Hibberd, P. L., & Gorbach, S. L. (2008). Probiotics for prevention of antibiotic-associated diarrhea. *Journal of Clinical Gastroenterology*, *42*(Suppl 2), S58–S63.

Duc le, H., Hong, H. A., Barbosa, T. M., Henriques, A. O., & Cutting, S. M. (2004). Characterization of Bacillus probiotics available for human use. *Applied and Environmental Microbiology*, *70*(4), 2161–2171.

Ewaschuk, J. B., Diaz, H., Meddings, L., Diederichs, B., Dmytrash, A., Backer, J., et al. (2008). Secreted bioactive factors from *Bifidobacterium infantis* enhance epithelial cell barrier function. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *295*(5), G1025–G1034.

Fang, H., Elina, T., Heikki, A., & Seppo, S. (2000). Modulation of humoral immune response through probiotic intake. *FEMS Immunology and Medical Microbiology*, *29*(1), 47–52.

FAO/WHO (2001). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Available from. http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf.

Fayol-Messaoudi, D., Berger, C. N., Coconnier-Polter, M. H., Lievin-Le Moal, V., & Servin, A. L. (2005). pH-, Lactic acid-, and non-lactic acid-dependent activities of probiotic Lactobacilli against *Salmonella enterica* Serovar Typhimurium. *Applied and Environmental Microbiology*, *71*(10), 6008–6013.

Fayol-Messaoudi, D., Coconnier-Polter, M. H., Moal, V. L., Atassi, F., Berger, C. N., & Servin, A. L. (2007). The *Lactobacillus plantarum* strain ACA-DC287 isolated from a Greek cheese demonstrates antagonistic activity in vitro and in vivo against *Salmonella enterica* serovar *Typhimurium*. *Journal of Applied Microbiology*, *103*(3), 657–665.

Foulquie Moreno, M. R., Sarantinopoulos, P., Tsakalidou, E., & De Vuyst, L. (2006). The role and application of enterococci in food and health. *International Journal of Food Microbiology*, *106*(1), 1–24.

Gaggia, F., Mattarelli, P., & Biavati, B. (2010). Probiotics and prebiotics in animal feeding for safe food production. *International Journal of Food Microbiology*, *141*(Suppl 1), S15–S28.

Galdeano, C. M., & Perdigon, G. (2006). The probiotic bacterium *Lactobacillus casei* induces activation of the gut mucosal immune system through innate immunity. *Clinical and Vaccine Immunology*, *13*(2), 219–226.

Galdeano, C. M., de Moreno de LeBlanc, A., Vinderola, G., Bonet, M. E., & Perdigón, G. (2007). Proposed model: Mechanisms of immunomodulation induced by probiotic bacteria. *Clinical and Vaccine Immunology*, *14*(5), 485–492.

Gauffin Cano, P., & Perdigón, G. (2003). Probiotics induce resistance to enteropathogens in a re-nourished mouse model. *The Journal of Dairy Research*, *70*(4), 433–440.

Gauffin Cano, P., Aguero, G., & Perdigón, G. (2002a). Immunological effects of yogurt addition to a re-nutrition diet in a malnutrition experimental model. *The Journal of Dairy Research*, *69*(2), 303–316.

Gauffin Cano, P., Aguero, G., & Perdigón, G. (2002b). Adjuvant effects of *Lactobacillus casei* added to a renutrition diet in a malnourished mouse model. *Biocell*, *26*(1), 35–48.

Gill, H. S. (2003). Probiotics to enhance anti-infective defences in the gastrointestinal tract. *Best Practice & Research. Clinical Gastroenterology*, *17*(5), 755–773.

Gill, H. S., Shu, Q., Lin, H., Rutherfurd, K. J., & Cross, M. L. (2001). Protection against translocating *Salmonella typhimurium* infection in mice by feeding the immuno-enhancing probiotic *Lactobacillus rhamnosus* strain HN001. *Medical Microbiology and Immunology*, *190*(3), 97–104.

Gillor, O., Etzion, A., & Riley, M. A. (2008). The dual role of bacteriocins as anti- and probiotics. *Applied Microbiology and Biotechnology*, *81*(4), 591–606.

Gobbato, N., Maldonado Galdeano, C., & Perdigón, G. (2008). Study of some of the mechanisms involved in the prevention against *Salmonella enteritidis* serovar Typhimurium infection by lactic acid bacteria. *Food and Agricultural Immunology*, *19*(1), 11–23.

Golowczyc, M. A., Mobili, P., Garrote, G. L., Abraham, A. G., & De Antoni, G. L. (2007). Protective action of *Lactobacillus kefir* carrying S-layer protein against *Salmonella enterica* serovar Enteritidis. *International Journal of Food Microbiology*, *118*(3), 264–273.

Henker, J., Laass, M., Blokhin, B. M., Bolbot, Y. K., Maydannik, V. G., Elze, M., et al. (2007). The probiotic *Escherichia coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. *European Journal of Pediatrics*, *166*(4), 311–318.

Hooper, L. V., & Macpherson, A. J. (2010). Immune adaptations that maintain homeostasis with the intestinal microbiota. *Nature Reviews. Immunology*, *10*(3), 159–169.

ISAPP (2002). International Scientific Association for Probiotics and Prebiotics. Retrieved january 10, 2011, from. http://www.isapp.net/docs/ProbioticDefinition.pdf 1.24.2011.

Jain, S., Yadav, H., Sinha, P. R., Naito, Y., & Marotta, F. (2008). Dahi containing probiotic *Lactobacillus acidophilus* and *Lactobacillus casei* has a protective effect against

Salmonella enteritidis infection in mice. *International Journal of Immunopathology and Pharmacology*, *21*(4), 1021–1029.
Jain, S., Yadav, H., & Sinha, P. R. (2009). Probiotic dahi containing *Lactobacillus casei* protects against *Salmonella enteritidis* infection and modulates immune response in mice. *Journal of Medicinal Food*, *12*(3), 576–583.
Kato, I. (2000). Antitumor activity of lactic acid bacteria. In R. Fuller, & G. Perdigón (Eds.), *Probiotics 3: Immunomodulation by the gut micgoflora and probiotics* (pp. 115–138). London: Kluwer Academic Publishers.
Komitopoulou, E., & Penaloza, W. (2009). Fate of *Salmonella* in dry confectionery raw materials. *Journal of Applied Microbiology*, *106*(6), 1892–1900.
Lara-Villoslada, F., Sierra, S., Boza, J., Xaus, J., & Olivares, M. (2007). Beneficial effects of consumption of a dairy product containing two probiotic strains, *Lactobacillus coryniformis* CECT5711 and *Lactobacillus gasseri* CECT5714 in healthy children. *Nutrición Hospitalaria*, *22*(4), 496–502.
LeBlanc, J. G., Matar, C., Valdez, J. C., LeBlanc, J., & Perdigon, G. (2002). Immunomodulating effects of peptidic fractions issued from milk fermented with *Lactobacillus helveticus*. *Journal of Dairy Science*, *85*(11), 2733–2742.
Lee, Y. K., Puong, K. Y., Ouwehand, A. C., & Salminen, S. (2003). Displacement of bacterial pathogens from mucus and Caco-2 cell surface by lactobacilli. *Journal of Medical Microbiology*, *52*(Pt 10), 925–930.
Lee, K., Lee, M., & Lee, Y. (2008). Safety assessment of commercial *Enterococcus* probiotics in Korea. *Journal of Microbiology and Biotechnology*, *18*(5), 942–945.
Lehloenya, K. V., Stein, D. R., Allen, D. T., Selk, G. E., Jones, D. A., Aleman, M. M., et al. (2008). Effects of feeding yeast and propionibacteria to dairy cows on milk yield and components, and reproduction*. *Journal of Animal Physiology and Animal Nutrition (Berlin)*, *92*(2), 190–202.
Lin, C. K., Tsai, H. C., Lin, P. P., Tsen, H. Y., & Tsai, C. C. (2008). *Lactobacillus acidophilus* LAP5 able to inhibit the *Salmonella choleraesuis* invasion to the human Caco-2 epithelial cell. *Anaerobe*, *14*(5), 251–255.
Lindhardt, C., Schonenbrucher, H., Slaghuis, J., Bubert, A., Ossmer, R., Junge, B., et al. (2009). Foodproof salmonella detection kit. Performance tested method 120301. *Journal of AOAC International*, *92*(6), 1876–1884.
Link-Amster, H., Rochat, F., Saudan, K. Y., Mignot, O., & Aeschlimann, J. M. (1994). Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. *FEMS Immunology and Medical Microbiology*, *10*(1), 55–63.
Liu, C., Zhang, Z. Y., Dong, K., Yuan, J. P., & Guo, X. K. (2009). Antibiotic resistance of probiotic strains of lactic acid bacteria isolated from marketed foods and drugs. *Biomedical and Environmental Sciences*, *22*(5), 401–412.
Liu, G., Griffiths, M. W., Wu, P., Wang, H., Zhang, X., & Li, P. (2011). Enterococcus faecium LM-2, a multi-bacteriocinogenic strain naturally occurring in "Byaslag", a traditional cheese of Inner Mongolia in China. *Food Control*, *22*(2), 283–289.
Macfarlane, G. T., & Cummings, J. H. (2002). Probiotics, infection and immunity. *Current Opinion in Infectious Diseases*, *15*(5), 501–506.
Mack, D. R., Michail, S., Wei, S., McDougall, L., & Hollingsworth, M. A. (1999). Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. *The American Journal of Physiology*, *276*(4 Pt 1), G941–G950.
Madsen, K., Cornish, A., Soper, P., McKaigney, C., Jijon, H., Yachimec, C., et al. (2001). Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology*, *121*(3), 580–591.
Makras, L., Triantafyllou, V., Fayol-Messaoudi, D., Adriany, T., Zoumpopoulou, G., Tsakalidou, E., et al. (2006). Kinetic analysis of the antibacterial activity of probiotic lactobacilli towards *Salmonella* enterica serovar Typhimurium reveals a role for lactic acid and other inhibitory compounds. *Research in Microbiology*, *157*(3), 241–247.
Maldonado Galdeano, C., & Perdigon, G. (2004). Role of viability of probiotic strains in their persistence in the gut and in mucosal immune stimulation. *Journal of Applied Microbiology*, *97*(4), 673–681.
Maldonado Galdeano, C., de Moreno de LeBlanc, A., Carmuega, E., Weill, R., & Perdigon, G. (2009). Mechanisms involved in the immunostimulation by probiotic fermented milk. *The Journal of Dairy Research*, *76*(4), 446–454.
Maragkoudakis, P. A., Chingwaru, W., Gradisnik, L., Tsakalidou, E., & Cencic, A. (2010). Lactic acid bacteria efficiently protect human and animal intestinal epithelial and immune cells from enteric virus infection. *International Journal of Food Microbiology*, *141*(Suppl 1), S91–S97.
Marianelli, C., Cifani, N., & Pasquali, P. (2010). Evaluation of antimicrobial activity of probiotic bacteria against *Salmonella enterica* subsp. enterica serovar Typhimurium 1344 in a common medium under different environmental conditions. *Research in Microbiology*, *161*(8), 673–680.
Marteau, P. R., de Vrese, M., Cellier, C. J., & Schrezenmeir, J. (2001). Protection from gastrointestinal diseases with the use of probiotics. *The American Journal of Clinical Nutrition*, *73*, 430–436.
Martins, F. S., Elian, S. D., Vieira, A. T., Tiago, F. C., Martins, A. K., Silva, F. C., et al. (2011a). Oral treatment with *Saccharomyces cerevisiae* strain UFMG 905 modulates immune responses and interferes with signal pathways involved in the activation of inflammation in a murine model of typhoid fever. *International Journal of Medical Microbiology*, *301*(4), 359–364.
Martins, A. K., Martins, F. S., Gomes, D. A., Elian, S. D., Vieira, A. T., Teixeira, M. M., et al. (2011b). Evaluation of in vitro antagonism and of in vivo immune modulation and protection against pathogenic experimental challenge of two probiotic strains of *Bifidobacterium animalis* var. lactis. *Archives of Microbiology*, *192*(12), 995–1003.
Mastroeni, P., & Maskell, D. (2006). *Salmonella infections: Clinical, immunological, and molecular aspects.* : Cambridge University Press.
Mastroeni, P., Grant, A., Restif, O., & Maskell, D. (2009). A dynamic view of the spread and intracellular distribution of *Salmonella enterica*. *Nature Reviews. Microbiology*, *7*(1), 73–80.
Mataragas, M., Skandamis, P. N., & Drosinos, E. H. (2008). Risk profiles of pork and poultry meat and risk ratings of various pathogen/product combinations. *International Journal of Food Microbiology*, *126*(1–2), 1–12.
McFarland, L. V. (2006). Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *The American Journal of Gastroenterology*, *101*(4), 812–822.
Medici, M., Vinderola, C. G., Weill, R., & Perdigon, G. (2005). Effect of fermented milk containing probiotic bacteria in the prevention of an enteroinvasive *Escherichia coli* infection in mice. *The Journal of Dairy Research*, *72*(2), 243–249.
Meyer, A. L., Elmadfa, I., Herbacek, I., & Micksche, M. (2007). Probiotic, as well as conventional yogurt, can enhance the stimulated production of proinflammatory cytokines. *Journal of Human Nutrition and Dietetics*, *20*(6), 590–598.
Miele, E., Pascarella, F., Giannetti, E., Quaglietta, L., Baldassano, R. N., & Staiano, A. (2009). Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *The American Journal of Gastroenterology*, *104*(2), 437–443.
Mountzouris, K. C., Balaskas, C., Xanthakos, I., Tzivinikou, A., & Fegeros, K. (2009). Effects of a multi-species probiotic on biomarkers of competitive exclusion efficacy in broilers challenged with *Salmonella enteritidis*. *British Poultry Science*, *50*(4), 467–478.
Mumy, K. L., Chen, X., Kelly, C. P., & McCormick, B. A. (2008). *Saccharomyces boulardii interferes with Shigella pathogenesis by postinvasion signaling events.* (0193–1857 (Print)).
O'Hara, A. M., O'Regan, P., Fanning, A., O'Mahony, C., Macsharry, J., Lyons, A., et al. (2006). Functional modulation of human intestinal epithelial cell responses by *Bifidobacterium infantis* and *Lactobacillus salivarius*. *Immunology*, *118*(2), 202–215.
O'Mahony, C., Scully, P., O'Mahony, D., Murphy, S., O'Brien, F., Lyons, A., et al. (2008). Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-kappaB activation. *PLoS Pathogens*, *4*(8), e1000112.
Pathmakanthan, S., Meance, S., & Edwards, C. A. (2000). Probiotics: A review of human studies to date and methodological approaches. *Medical Ecology in Health and Disease*, *2*, 10–13 (supplement).
Perdigón, G., Alvarez, S., N.de Macías, M. E., & Medici, M. (1989). Effect of lactic acid bacteria orally administered and of yogurt on the immune system. *Les Laits Fermentes; Actualite de la Recherche* (pp. 77–89). Paris: Libbey.
Perdigón, G., Alvarez, S., N.de Macías, M. E., & P.de Ruiz Holgado, A. (1990). The oral administration of lactic acid bacteria increase the mucose intestinal immunity in response to enteropathogens. *Journal of Food Protection*, *53*, 404–411.
Perdigón, G., N.de Macías, M. E., Alvarez, S., Oliver, G., & P. de Ruiz Holgado, A. (1990). Prevention of gastrointestinal infection using immunobiological methods with *L. casei* and *L. acidophilus* fermented milk. *The Journal of Dairy Research*, *57*, 255–262.
Perdigón, G., Alvarez, S., de Macías, M. E., S. de Giori, G., Medici, M., & N. de Kairuz, M. (1991). Behaviour of natural and heated yogurt in the immune system and preventive capacity on enteric infections. *Milchwissenschaft*, *46*, 411–416.
Perdigón, G., Alvarez, S., & P. de Ruiz Holgado, A. (1991). Immunoadjuvant activity of oral *Lactobacillus casei*: Influence of dose on the secretory immune response and protective capacity in intestinal infections. *The Journal of Dairy Research*, *58*(4), 485–496.
Perdigón, G., Alvarez, S., Medici, M., & P. de Ruiz Holgado, A. (1993). Influence of the use of *Lactobacillus casei* as an oral adjuvant on the levels of secretory immunoglobulin A during an infection with *Salmonella typhimurium*. *Food and Agricultural Immunology*, *5*(1), 27–37.
Perdigón, G., Rachid, M., De Budeguer, M. V., & Valdez, J. C. (1994). Effect of yogurt feeding on the small and large intestine associated lymphoid cells in mice. *The Journal of Dairy Research*, *61*(4), 553–562.
Perdigón, G., Alvarez, S., Gobbato, N., de Budeguer, M., & P. de Ruiz Holgado, A. (1995). Comparative effect of the adjuvant capacity of *L. casei* and LPS on the intestinal secretory antibody response and resistance to *Salmonella* infection in mice. *Journal Agricultural Immunology*, *7*, 283–294.
Perdigón, G., Maldonado Galdeano, C., Valdez, J. C., & Medici, M. (2002). Interaction of lactic acid bacteria with the gut immune system. *European Journal of Clinical Nutrition*, *56*(Suppl 4), S21–S26.
Podolak, R., Enache, E., Stone, W., Black, D. G., & Elliott, P. H. (2010). Sources and risk factors for contamination, survival, persistence, and heat resistance of *Salmonella* in low-moisture foods. *Journal of Food Protection*, *73*(10), 1919–1936.
Rajashekara, G., Haverly, E., Halvorson, D. A., Ferris, K. E., Lauer, D. C., & Nagaraja, K. V. (2000). Multidrug-resistant *Salmonella* Typhimurium DT104 in poultry. *Journal of Food Protection*, *63*(2), 155–161.
Shu, Q., Lin, H., Rutherfurd, K. J., Fenwick, S. G., Prasad, J., Gopal, P. K., et al. (2000). Dietary *Bifidobacterium lactis* (HN019) enhances resistance to oral *Salmonella typhimurium* infection in mice. *Microbiology and Immunology*, *44*(4), 213–222.
Silva, A. M., Barbosa, F. H., Duarte, R., Vieira, L. Q., Arantes, R. M., & Nicoli, J. R. (2004). Effect of *Bifidobacterium longum* ingestion on experimental salmonellosis in mice. *Journal of Applied Microbiology*, *97*(1), 29–37.
Totemeyer, S., Foster, N., Kaiser, P., Maskell, D. J., & Bryant, C. E. (2003). Toll-like receptor expression in C3H/HeN and C3H/HeJ mice during *Salmonella enterica* serovar Typhimurium infection. *Infection and Immunity*, *71*(11), 6653–6657.
Valdez, J., Rachid, M., Gobbato, N., & Perdigón, G. (2001). Lactic acid bacteria induce apoptosis inhibition in *Salmonella typhimurium* infected macrophages. *Food and Agricultural Immunology*, *13*, 189–197.
Vanderhoof, J. A. (2008). Probiotics in allergy management. *Journal of Pediatric Gastroenterology and Nutrition*, *47*(Suppl 2), S38–S40.
Vinderola, G., Matar, C., & Perdigón, G. (2005). Role of intestinal epithelial cells in immune effects mediated by Gram-positive probiotic bacteria: Involvement of toll-like receptors. *Clinical and Diagnostic Laboratory Immunology*, *12*(9), 1075–1084.

Vinderola, G., Perdigón, G., Duarte, J., Farnworth, E., & Matar, C. (2006). Effects of the oral administration of the products derived from milk fermentation by kefir microflora on immune stimulation. *The Journal of Dairy Research*, *73*(4), 472–479.

Vinderola, G., Matar, C., & Perdigon, G. (2007). Milk fermented by *Lactobacillus helveticus* R389 and its non-bacterial fraction confer enhanced protection against *Salmonella enteritidis* serovar Typhimurium infection in mice. *Immunobiology*, *212*(2), 107–118.

Wagner, R. D., Johnson, S. J., & Kurniasih Rubin, D. (2009). Probiotic bacteria are antagonistic to *Salmonella enterica* and *Campylobacter jejuni* and influence host lymphocyte responses in human microbiota-associated immunodeficient and immunocompetent mice. *Molecular Nutrition & Food Research*, *53*(3), 377–388.

Wallis, T. S., & Galyov, E. E. (2000). Molecular basis of *Salmonella*-induced enteritis. *Molecular Microbiology*, *36*(5), 997–1005.

Watson, R. R., & Preedy, V. R. (2010). *Bioactive foods in promoting health: Probiotics and prebiotics.* : Academic Press.

Wohlgemuth, S., Loh, G., & Blaut, M. (2010). Recent developments and perspectives in the investigation of probiotic effects. *International Journal of Medical Microbiology*, *300*(1), 3–10.