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Lactobacillus casei Shirota and Inflammatory Biomarkers: A Literature Review

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This review aims to study the rol of *Lactobacillus casei* Shirota (*Lc*S) in inflammatory biomarkers. In the last decade, the association between the consumption of probiotics and their effect on health has been shown. For example, they have been proposed as a reliable tool for modulating the intestinal microbiota and a potential therapy for specific disorders or diseases. In this regard, research on the use of *Lc*S has gained significant interest, with a wide variety of studies conducted in cellular, murine, and human models. In general, it has been observed that the best results on inflammatory biomarkers are obtained with the consumption of *Lc*S together with other substances, such as prebiotics, in cellular and murine models; while in human models, the best results are obtained in studies with healthy subjects. An area of opportunity arises for the clinical use of *Lc*S together with other substances, to reduce inflammatory markers, given that this strategy provides better results in cellular or murine models, and to date, there are a few human studies with this type of intervention. There is sufficient evidence about the consumption of probiotics and their effects on health, since their historical use in fermented foods (mainly milk), makes them culturally acceptable by the population and in important efforts by the scientific community to continue contributing to the description and efficacy of their use, thereby understanding the various bacteria involved, such as Bacteroidetes. Research designs are diverse and nonspecific, in addition to the mechanisms linked to differences in their effectiveness with their use, such as the kind of foods, age, gastrointestinal pH, physical activity, etc., in addition to the type of foods that have a prebiotic function, which makes it difficult to measure the same result or benefit. This makes them confounding variables that need to be controlled and analyzed in studies. Therefore, it is important to continue contributing to clarifying their benefits and in what types of pathologies, duration of treatment, doses, etc. It becomes imperative to continue conducting clinical studies on different pathologies as has been done and considering diet, from its combination, quality and quantity.

Keywords: Interleukin-6; Inflammation markers; *Lactobacillus casei* Shirota; Probiotics; Tumor Necrosis Factor-alpha.

To understand the relationship between the microbiota and the human immune system has become a significant topic of interest due to its relationship with diseases with an inflammatory component.[1] Most research focuses on the correlation between changes in microbiota

composition and various pathological states that lead to dysregulation of bodily functions.[2-5]

The cross-talk capacity between the gut microbiota and the immune system is necessary to enable bacterial priming and immune system maturation, especially in early life, as 70% of immune cells reside in the gut; such interactions contribute to lifelong homeostasis.[6]

Throughout life, the intestinal microbiota faces various disturbances (unhealthy diet, drugs, alcohol, intense exercise, pathogenic bacteria),[5,7] where if it is not able to overcome, a change occurs that leads to a new balance that may not be healthy, called dysbiosis, which promotes greater intestinal permeability, which conditions endotoxemia and subsequent systemic inflammation.[7,8] This is a consequence of the deterioration of the structure and function of the intestinal barrier.[8,9]

Following the advent of understanding the close relationship between the gut microbiota and various physiological and metabolic processes, manipulation of the gut microbiota has gained interest among the scientific community to prevent or treat diseases.[1,6]

In general, probiotics and prebiotics are the most popular topics in microbiota modulation research. It is suggested that the administration of probiotics improves the composition of the intestinal microbiota, regulating dysbiosis and homeostatic balance in the gastrointestinal tract, preventing the colonization of pathogens, and restoring stability, resilience, and symbiotic interaction with the host.[1]

Among the probiotics, *Lactobacillus casei* Shirota (*Lc*S) stands out, since it has been commonly used in the production of probiotic dairy products as a food ingredient. [10] In addition, its role in reducing inflammatory markers, molecules associated with several pathological entities has been evaluated in vitro, in vivo, and ex vivo models with a great diversity of study designs and models used. In general, it has been observed that it reduces inflammatory markers, improving health.

MATERIALS AND METHODS

A literature review was designed, searching articles on *Lc*S and inflammation markers in PubMed®, Google Schoolar®, and Scopus®, with the words: Probiotics, *LcS*, AND effects on health, or AND inflammation markers.

The authors reviewed the articles obtained to check if they included the effects on health, on inflammation markers, and the mechanisms for those effects from *Lc*S.

RESULTS

Gut microbiota alterations and inflammation

Digestive tract as an immune organ

The digestive tract has a large surface area of approximately 32 m², equivalent to half a badminton court,[11] which is in constant contact with external antigens such as those from food, ingested pathogens, and microorganisms from the intestinal microbiota. Despite this, only a thin layer of intestinal epithelial cells (IECs), tightly linked by intercellular tight junctions (ITJ) proteins, separates these elements from the interior of the organism[12] and maintains the integrity of the epithelial barrier and cell polarity.[13] In addition, IECs express various receptors for pathogen recognition, the most prominent of which are Toll-like receptors (TLR), whose location dictates the response of the immunology system. These can trigger inflammatory responses if activated by their ligand.[14] An example of this is TLR4, which has a low response to lipopolysaccharide (LPS) from bacteria present in the digestive tract, providing tolerance to these stimuli. TLR5, which is expressed in the basolateral wall of epithelial cells, mounts a response against bacteria that invade this space.[14]

In addition to these functional barriers, the digestive system houses the body's most extensive and complex immune system, whose characteristics allow for effective defense against microorganisms. This system has unique characteristics, as it maintains tolerance to food antigens and commensal microbiota, but at the same time, it allows for an effective response against pathogenic microorganisms.[15]

The immune system in gastrointestinal tract is composed of a variety of specialized cells, including M cells, responsible for the uptake of luminal antigens; Paneth cells, which produce defensins; immunoglobulin (Ig)A and IgM-secreting cells, which neutralize microbes in the

Table 1. Literature on the use of *Lc*S and inflammation markers on basic science

Dong, et al.[47]	Human Healthy older adults aged 55-74	30 Adults (18/12)	1. Treated with *LcS* (n=16) 2. Placebo (n=14)	1. Probiotic drink (65 ml) with 1.3 x 10 10 CFU, 2 bottles per day 2. Skimmed milk (130 mL), per day	14 weeks of treatment, followed by 4 weeksof rest Peripheral blood and saliva samples were collected at the beginning and end of each period.	↑ IL-10/IL-12 ratio
Kaya MS, et al.[48]	Animal Male Wistar Albino rats all with obesity induced	total=110 50 young (2 months old) 60 old (16 months old)	1. Control 2. Food restriction 3. Probiotic supplement (*LcS*) 4. Exercise. Each group contained old and young rats	1. For the feed restriction group, they ate 40% less than the rest. 2. The exercise group was allowed to exercise 21 m/min speed at 15% incline, The exercise group did it for 5 days a week on a treadmill device for 16 weeks	16-week treatments	Effects of *LcS* on Biomarkers Old Mice: ↑ IL-12 and IGFBP-3 ↓ IL-6 Young Mice: ↑ IL-12 and IGFBP-3 ↓ IL-6
Falasca K[49]	Human and Cellular HIV-positive men on antiretroviral therapy and PBMNC from participants	30 (30/0)	1.Treated with LcS (n=30)	One bottle of fermented milk Yakult Light® containing *LcS* twice a day (containing a minimum of 6.5 × 109 CFU LcS)	Four weeks. There were measures before and after the four weeks.	Serum Cytokine Levels before and after *LcS* intake: ↓ IL-23 *LcS* on gene expression of the cytokines in PBMNC: ↓ mRNA levels of TGFβ, IL-10 and IL-12 ↑ levels of IL-4 mRNA ↓ IL-1β expression *LcS* on Cytokine Production by PBMNC: ↑ TGFβ
Harbige et al.[50]	Human Healthy adults ages 18-49	18 (8/10)	1. Treated with *LcS* (n=14) 2. Not treated with *LcS* (n=4)	1. Drink (65 ml) with 1.3 x 1010 live *LcS* cells, 2 bottles per day	Primary intake (priming) period of 4 weeks, followed by 6 weeks of interruption and a secondary intake (booster) period of 4 weeks	Ex vivo stimulated blood cells: ↓ IL-4 at week 14 ↓ IL-12 at weeks 4, 10, and 14 ↓ TNF-α at weeks 4, 10, and 14 Unstimulated ex vivo blood cells: ↓ IL-4 at weeks 10 and 14 ↓ IL-12 at weeks 4, 10, and 14
Matsumoto S, et al.[42]	Celular -Female BALB/c mice (8 weeks age) -SAMP1/Yit mice (15 weeks of age -C3H SCID mutant mice (C3H/SmnC Prkdc scid/J, 10 weeks of age)	-	1. Mice treated with DSS induced colitis and *LcS* 2. Mice treated with DSS induced colitis and different strains of lactobacilli. PSPG of LcS were also isolated and used.	1. Induction of Chronic DSS Four cycles of drinking water with DSS, each cycle was with 4% DSS. 2. In-Vitro IL-6 inhibition The PBMNC cells stimulated with with LPS at a 100/ ng/ml concentration. There were different concentrations of *LcS*, as well mutant *Lactobacilli and* PSPG complex.	1. Induction of Chronic DSS colitis 56 days for the induction 2. In-Vitro IL-6 inhibition For 24 hours *LcS* and its components were added to LPMCs, RAW264.7 cells, and IBD PBMNC	LcS-derived PSPG complex: £" IL-6 production in LPS-stimulated LPMCs from mice with induced colitis PSPG-I and PS-I ↓ the production of IL-6 in LPS-stimulated RAW cells., PSPG-I £" phosphorylation of NF-κB.

Dong H, et al.[45]	Celular Human PBMNC in vitro	-	1. LcS at different concentrations (a, b, c) with or without ConA 2. LcS at different concentrations (a, b, c) with or without LPS	*Lcs concentrations* *a.LcS: 105 UFC/ml* *b.LcS: 106 UFC/ml* *c.LcS:107 UFC/ml* *1.ConA: 2.5 µg/ml* *2.LPS: 1 µg/ml*	24 hours	The *LcS* enhances the lymphocyte activation of cytotoxic T (CD8+ T cells). *LcS*: ↑ IL-1β, IL-6, TNF-α, IL-12 and IL-10 *LcS* + LPS: £" IL-10 and IL-6 production
Dong H. et al [46]	Celular PBMNC from from 19 healthy adult donors aged between 28 and 44 years		1. PBMNC incubated with LcS at different concentrations (a, b, c) with or without ConA 2. PBMNC incubated with LcS at different concentrations (a, b, c) with or without LPS	Concentration of *LcS*: a.*Lc*S: 105 UFC/ml b.*Lc*S: 106 UFC/ml c.*Lc*S:107 UFC/ml 1.. ConA: de 2,5 ìg/ml. 2. LPS: 1 µg/m	1. PBMNC was incubated for 24h with *LcS*. 2. 24 hours of incubation with *LcS* in the presence or absence of ConA or LPS for monocyte depletion experiments, PBMNC or MD-PBMNCs	*LcS* ↑ CD69 expression on CD4+ and CD8+ lymphocytes ↑ CD25 expression in CD8+ lymphocytes ↑ IL-1β and IL-12 ↑* IL-6 and IL-10 ↑** TNF-α LPS ~ IL-12 ↑* IL-1β and TNF-α ↑** IL-6 and IL-10 *LcS* + LPS ~ IL-12 ↑* IL-6 and TNF-α ↑** IL-10 and IL-8
Kaji R, et al.[51]	Celular Peritoneal macrophages prepared from BALB/c mice.	-	Macrophages in the presence or absence of heat-killed lactobacilli and each TLR ligand. 1. Macrophages without *LcS and TLR ligands* TLR ligands:-Lipoteichoic acid (LTA): TLR2 ligand - Poly (I:C): TLR3 ligand) - LPS: TLR4 ligand- Flagellin: TLR5 ligand -Gardiquimod: TLR7 ligand - CpG-DNA: TLR9 ligand Heat-killed lactobacilli:- *LcS* - *L. Johnsonii*	Macrophages in a 96-well culture plate with 0.2 mL of RPMI 1640 medium supplemented with 10% fetal calf serum Each TLR ligand: 1 ìg/mL Heat-killed lactobacilli (10 ìg/mL)	24 hours.	*LcS:* ↑** IL-12 ↑* IL-10 *LcS* + TLR3 and TLR5 ligand*:* ↑ IL-12 production relative to LcS alone. *LcS* + TLR2, TLR4, TLR7, and TLR9: ↑ IL-10 production £" IL-12 production induced by LcS alone.
Vaisberg, et al.[52]	Human Marathon runners from the city of São Paulo and its surrounding areas.	42 (42/0)	1. Placebo (n=22) 2. Treated with *LcS* (*LcS*) (n=20)	1. Fermented milk (80 grams) without *LcS*, daily. 2. Fermented milk (80 grams) with 10 x 109 live *LcS* cells, daily.	30 days Blood, saliva, and nasal mucosa samples were collected at five-time points: before and after 30 days of	Salivary samples: The *LcS* were able to maintain IgA and antimicrobial peptide levels. Nasal mucosal lavage: ↑ IL-10, leading to a higher nasal

					ingestion of fermented milk or placebo, 24 hours before the competition, 72 hours, and 14 days after the competition.	IL-10/IL-12p70 ratio. ↓ Proinflammatory cytokines (IL-1, IL-5, IL-6, IL-13, and TNF-α). ↓ Neutrophil infiltration in the nasal mucosa. Blood samples: ↓ TNF-α immediately after the marathon.
Macnaughtan et al.[53]	Human Patients with cirrhosis and Child-Pugh scores <10	92(62/30)	1. Treated with *LcS* (n=46) 2. Placebo (n=46)	1. Drink (65 ml) with 6.5 x 109 CFU of *LcS*, 3 times a day 2. Drink with similar appearance and taste, without bacteria, 3 times a day	6 months Screening at, days 0 and 14, and months 1, 3 and 6.	Patients with alcoholic cirrhosis: ↓ mean plasma concentrations of IL-1B and MCP-1. Patients with non-alcoholic cirrhosis: ↓ IL-17[a]
Mai C, et al.[54]	Animal ICR mice (10-week-old males from Shanghai, China). They were fed regularly for one week with unlimited access to food, with temperature and humidity controlled.	120	1. Control (no sepsis) (n=20) 2. Model (sepsis without treatment) (n=20) 3. *LcS* (n=20) 4. Geniposide 5. *LcS* + Geniposide (n=20) 6. Dexamethasone (n=20)	1. the *LcS* group mice were treated with *LcS* (5 × 107 colony-forming unit (CFU)/kg) by gavage 2. The geniposide group mice were treated with geniposide (50 mg/kg, purity 99.9% 3. Dexamethasone (1 mg/kg) by intraperitoneal injection and treated with normal saline (0.2 ml) by gavage To induce sepsis in the mice, the cecum was ligated and perforated	1 week administration of *LcS* One week later, tissue and blood samples were taken and analyzed	In every group with sepsis mice, they had an elevation of inflammatory biomarkers in the hypothalamus Model: ~ TNF-α, IL-6, IL-1B *LcS:* ↓* TNF-α, IL-6, IL-1B Geniposide: ↓* TNF-α, IL-6, IL-1B *LcS* + Geniposide ↓** TNF-α, IL-6 and IL-1B
Yan, et al.[55]	Animal Specific pathogen-free (SPF) Sprague Dawley rats (Shanghai SLAC Laboratory Animal Co. Ltd., Shanghai, China)	120 (120/0)	1. Healthy control (HC) (n=8) 2. Positive control (PC) (n=8) Treated with LcS (LcS), 3. Treated with LcS (LcS) (n=8)	1. 1 ml of freshly prepared LcS suspension (3 x 109 CFU) by intragastric administration, daily 2. 1 ml of saline solution, daily 3. 1 ml of saline solution daily	7 days On the eighth day, ALI was induced in the rats in the *LcS* and PC groups by intraperitoneal injection of D-GalN (Sigma, Saint Louis, MO, USA) at a dose of 1.1 g kg-1 body weight, while the rats in the HC group received the same dose of saline.	↓ IL-5, IL-10, and RANTES ↓ transcriptional upregulation of inflammatory genes such as CcI11, Lif, and II11in the liver Partially prevented D-GaIN-induced alterations in the gut microbiota.

ConA: Concanavalin A, PBMNC: Peripheral Blood Mononuclear Cells, IBD: Inflammatory Bowel Disease, LcS: *Lactobacillus casei* Shirota, LPS: Lipopolysaccharide, PLMC: Lamina Propia Mononuclear Cells, PSPG: Cell wall-derived polysaccharide-peptidoglycan complex, PS-I: Polysaccharide Fraction - I, DSS: Sodium Dextran Sulfate, CFU: Colony Forming Units. ?: Inhibits, ~: No change, ↓: Decrease, ↓*: Weak decrease, ↓**: Strong decrease, ↑: Elevation, ↑*: Weak elevation, ↑**: Strong elevation.

intestinal lumen; and subsets of dendritic cells (DC), which are involved in the recognition and processing of antigens.[12,15]

One of the DC subtypes, lamina propria DCs, can respond to TLR stimulation, producing interleukin-10 (IL-10) and little or nothing of IL-12, therefore, selective regulation of TLRs is critical for the modulation of inflammatory responses.[14]

Normal microbiota and its interaction with the immune system

Under healthy conditions, the gut microbiota possesses stability, and resilience it establishes a symbiotic relationship with the host[1] protecting it against infections and other pathologies by inhibiting microbial invasion and/or helping to orchestrate optimal immune responses.[16] In addition, it helps to supplement essential nutrients, participates in vitamin K synthesis, favors cellulose digestion, and promotes angiogenesis and enteric nerve function.[17]

These benefits are obtained thanks to the joint work of trillions of bacteria of different species that cover the entire surface of the digestive tract.[16] Among these, the phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria* stand out mainly.[18]

However, the composition is not static and can change according to different external factors such as diet, medications, age, host factors (pH, bile acids, pancreatic enzymes, mucus composition, and transit time), and bacterial factors (adhesion capacity, enzymes, and metabolic capacities).[4,6,19]

These changes in the composition of the microbiota can condition alterations in the immune response since this contributes to the development and regulation of the immune system.[19,20] In this sense, Ly NP, et al.,[21] found a positive correlation between the presence of gram-positive anaerobes (*Lactobacilli* and *Bifidobacteria*) and gram-negative anaerobes (*Bacteroides* and *Prevotella* spp) in maternal feces and the secretion of IL-10 by umbilical cord blood mononuclear cells. It is well known that IL-10 plays a vital role in the regulation of the immune response since it favors the maturation of regulatory T lymphocytes (RTL).[6,22]

Different cells of the immune system express receptors for products of bacterial metabolism in the gastrointestinal tract. Among these, short-chain fatty acids (SCFA) are the main metabolites with immunomodulatory characteristics; since their absence or presence influences the activity of various immune cells, including RTL, tolerogenic DC, tolerogenic macrophages, tolerogenic Natural Killer (NK) cells, and CD4+ T lymphocytes of the T helper (Th) 1, Th2, and Th17 subtypes, among others.[23]

Dysbiosis and its relationship with systemic inflammation

Intestinal dysbiosis is a condition in which the ecosystem where beneficial intestinal bacteria live is not in harmony with its environment, altering the homeostasis and normal regulation of digestion, metabolism, and immune modulation.[4,5] Dysbiosis is considered to be the result of multiple factors, such as diet, stress, and genetic defects, as well as the consumption of alcohol and medications (antibiotics and non-antibiotics).[5,7]

Modifications in the composition and functionality of the microbiota mainly characterize this.[4,5] One of the most frequent changes in composition is the increase of up to 20-30% of *Proteobacteria*, such as *Escherichia Coli* and *Klebsiella* spp, while in healthy individuals, they represent less than 10%.[5]

Dietary patterns directly modify the composition and functionality of the intestinal microbiota.[7] It has been found that a Western diet, characterized by being rich in refined sugars, animal fats, and processed meats, has a close relationship with intestinal dysbiosis and inflammation.[24] This type of diet conditions an increase in intestinal permeability, with the consequent leakage of toxic bacterial metabolites such as LPS, which when passing into the systemic circulation can condition low-grade inflammation both locally and systemically.[24-26]

LPS, upon binding to its ligands TLR4 and CD14, triggers a signaling pathway that leads to the expression of proinflammatory cytokines.[25,27,28] This pathway leads to the activation of various molecules, such as myeloid differentiation primary response 88 (MyD88) and MAL, which in turn stimulate the activation of transcription factors such as nuclear factor-kappa B (NF-êB) and activator protein-1 (AP-1); NF-êB activation promotes the nuclear transcription of proinflammatory cytokines,

including tumor necrosis factor alpha (TNF-á), IL-1â, IL-6, and IL-8, which play a key role in the inflammatory response.[28]

As a consequence of the relationship between alterations in the microbiota and a wide variety of pathologies with an important inflammatory component,[26] the modulation of the former through the use of probiotics has gained special interest, since these could improve the intestinal microbiota, increase mucus secretion and prevent the destruction of TJs by decreasing LPS.[6]

Probiotics

History of probiotics

The history of probiotics is as old as humanity itself, with the first foods containing live microorganisms, such as fermented milk, originating in the ancient Egyptians, Phoenicians and other Eastern cultures.[29]

Throughout history and since time immemorial, there have been numerous descriptions and evidence of the use of fermented beverages in different cultures around the world, long before the existence of bacteria was known.[29]

The health-promoting properties of these dairy products were part of folklore until the emergence of the concept of probiotics, which gave a systematic approach to the study of these foods. The first definition of probiotics dates to 1953, established by Werner Kollath, a German scientist, who designated probiotics as "active substances essential for the healthy development of life".[29]

Since then, various descriptions have been coined, leading to the Food and Agriculture Organization and the World Health Organization (FAO/WHO) proposal that defines probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host".[30]

Development and New Perspectives

In recent years, a growing number of studies have revealed the benefits of probiotics and fermented products for human well-being. Therefore, their applications in foods, medicines, and other functional products have gained increasing attention.[31]

Probiotic therapy involves the targeted introduction of beneficial microorganisms into the intestinal flora. This causes beneficial and harmful bacteria to compete for nutrients,[32] affecting the host's metabolism.[33]

These microorganisms, composed mainly of bacteria and yeast, are present in some fermented foods (e.g., yogurt) and are added to some food products marketed as dietary supplements.[34] The latter come in various forms (capsules, powders, liquids) and can contain a wide variety of strains and doses.[30,34,35]

The effects of probiotics vary and depend on the type, dose, and their interaction with the host.[32] Three different mechanisms can explain the mechanisms by which the use of probiotics confers health benefits:

1. Nonspecific mechanisms: These vary among strains, species, and genera. Inhibition of the growth of pathogenic microorganisms, production of bioactive metabolites (e.g., SCFAs), reduction of colonic luminal pH, regulation of intestinal transit, and normalization of the microbiota have all been described.[30,34]
2. Species-specific mechanisms (frequent): Vitamin synthesis, reinforcement of the intestinal barrier, bile salt metabolism, enzymatic activity, and toxin neutralization.[30,34]
3. Strain-specific mechanisms (rare): Cytokine production, specific immunomodulatory activities, effects on the endocrine and nervous systems, and the production of specific bioactive ingredients.[30,34]

The most common strains currently available as probiotics and that have beneficial effects on health are *Enterococcus faecium*, *Bifidobacterium*, *Bacillus*, *Saccharomyces boulardii*, *Lactobacillus*, and *Pediococcus* strains.[32] Counting on more recent candidates such as *A. muciniphila* and *Faecalibacterium prausnitzii*.[33] Within these, lactic acid bacteria (LAB) derived from *Lactobacillus* and *Enterococcus* are the most popular probiotics today.[31]

***Lactobacillus casei* Shirota**

Lactobacillus is the largest genus in the family *Lactobacillaceae*.[35] These species are not only isolated from environments related to fermented foods (fruits, meat, sourdough, vegetables, wine) but also from the gastrointestinal and vaginal tracts of humans and animals.[36-38]

Lactobacilli are gram-positive, rod-shaped, facultatively anaerobic or croaerophilic, non-spore-forming, acid-tolerant, catalase-negative bacteria with DNA content.[35] They constitute the largest and most diverse genus of lactic acid bacteria,[39] which are known for

their ability to produce substantial amounts of bioactive compounds during fermentation, such as exopolysaccharides, bacteriocins, amylases, proteases, and lipases.[31]

*Lc*S is a strain of lactic acid bacteria that has been widely used in the production of probiotic dairy products and also as food ingredients.[36] As the mechanisms behind their health-promoting capabilities are unraveled, potential applications for these strains in the fields of food, biotechnology, and medicine are being developed.[40]

Clinical efficacy may not be mediated solely by the increase in the host immune response, as several studies in animal models suggest that *Lc*S-induced activation of immunocompetent cells plays a key role.[41]

***Lactobacillus casei* Shirota, and Inflammation**

*Lc*S is one of the most widely distributed probiotics on the market and has been tested in different studies to evaluate its impact on health. Among these, its effects on immunomodulation and inflammatory markers have been a source of great interest for the scientific community. However, the designs of these studies are very diverse; on the one hand, *Lc*S has been studied individually or in conjunction with a prebiotic, a compound known as a symbiotic.[42] The study model has also been different, as it has been tested in in vitro, in vivo and ex vivo models, particularly in cellular models where peripheral blood mononuclear cells derived from animals and humans are studied.

Table 1 shows a summary of the scientific evidence on the study of the role of *Lc*S on inflammatory markers, in animal, human or in vitro models.

DISCUSSION

Effects of *Lc*S on inflammatory biomarkers in vitro models

The effects of *Lc*S on inflammation are varied and depend on both its concentration and the presence of other molecules. Numerous studies have shown that *Lc*S alone can induce the expression of various inflammatory markers in cellular models, including IL-1â, IL-6, TNF-á, IL-12, and IL-10.[42,44-46,51] In a study conducted in PBMNC by Shida K. et al.,[43] the inflammatory response induced by *Lc*S was observed to be dose-dependent. At high concentrations, a marked induction of TNF-á and IL-10 is recorded, along with reduced expression of IL-12 and IFN-ã. In contrast, at low concentrations, a mild elevation of TNF-á and IL-10 is observed, but increased production of IL-12 and IFN-ã is observed.

It is worth noting that these cytokines play both pro-inflammatory and anti-inflammatory roles. In particular, IL-10 is a key cytokine in the induction of RTL, which modulates the inflammatory response.[6,21] Likewise, cytokines such as IL-6, TNF-á, and IL-12 are essential for initiating the inflammatory cascade mediated by the transcription factor NF-êB and MyD88.[28] In this regard, Shida K et al.,[44] in their study of MyD88-deficient mice, did not observe an increase in IL-12 after stimulation with *Lc*S.

Furthermore, *Lc*S-induced cytokine expression is highly dependent on the microenvironment surrounding the stimulated cells and dictates the pathway toward a pro-inflammatory and/or anti-inflammatory state. The main factor identified that modulates such expression is the TLR4 receptor activated by LPS.[42,44-46,51] On its own, LPS is a potent inducer of inflammatory cytokines such as IL-6, IL-12, and TNF-á;[44,46] however, TLR4-mediated proinflammatory cellular activation, when *Lc*S is administered, shows a lower expression of cytokines such as IL-6 and IL-12.[44-46,51]

One of the main components of *Lc*S involved in this effect is the cell wall-derived polysaccharide-peptidoglycan (PSPG) complex, composed of PSPG-I, PSPG-II, and the polysaccharide fractions (PS -I and PS-II). In this regard, Matsumoto et al.,[42] evaluated these compounds in a murine model of induced colitis, stimulating LPMC cells with LPS. In their study, they observed that PSPG-I and PS-I inhibited IL-6 production; furthermore, PSPG-I alone also inhibited NF-êB phosphorylation.

On the other hand, Dong, et al.,[46] conducted a study in human PBMNC in which they observed that the combination of *Lc*S with LPS induced a marked increase in immunomodulatory cytokines such as IL-1â and IL-10, while reducing the expression of IL-6, IL-12, and TNF-á, compared to the individual administration of *Lc*S or LPS, which presented a predominantly proinflammatory profile.

Similarly, Kaji R.,[51] evaluated TLR4 activation in combination with *Lc*S; however, he also analyzed the effect of TLR3, TLR5, TLR7, and TLR9 together with their ligands; his study revealed that TLR2, TLR4, TLR7, and TLR9 ligands induced IL-10 expression and inhibited IL-12 production, whereas TLR3 and TLR5 ligands were associated with an increase in IL-12 expression.

From the above, it can be inferred that cellular models allow us to investigate the direct effect of *Lc*S on the production of cytokines in a controlled manner, together with the presence of different bacterial components such as LPS, lipoteichoic acid, flagellin, and the activation of their corresponding TLRs.[44-46,51]

Effects of *Lc*S on Biomarkers of Inflammation in vivo in Murine Models

The effects of *Lc*S in mouse models are of particular interest, as these systems are more complex than cellular models, making it difficult to measure or control all the variables involved precisely. Furthermore, these types of models more closely resemble human studies, allowing for interventions that would be impossible in human models, but also to measure or control all the variables involved precisely allowing for a more in-depth understanding of the effects of *Lc*S in complex environments.

Kaya et al.,[48] evaluated the effect of *Lc*S in a murine model using young and old mice. After administration, they observed an increase in the levels of IL-12 and IGFBP-3, as well as a decrease in the expression of IL-6 in both groups. In addition, they compared the effect of *Lc*S with other interventions, such as food restriction, and exercise, and established a control group. In old mice, *Lc*S was the intervention that most reduced IL-6 levels, while in young mice it was the one that most increased the expression of insulin-like growth factor binding protein-3 (IGFBP-3). In old mice, on the other hand, it was the one that most elevated IL-12.[48]

For their part, Mai, et al.,[54] evaluated the effect of *Lc*S in combination with geniposide in a murine model of induced sepsis, showing that *Lc*S, on its own, produced a modest reduction in the levels of TNF-á, IL-6, and IL-1â in the hippocampus of mice; however, when administered together with geniposide, a significant decrease in these proinflammatory cytokines was observed, as well as a notable reduction in mortality. It is suggested that this synergistic effect is due to the presence of the enzyme â-glucosidase in *Lc*S, which allows the conversion of geniposide into genipin, a compound with potent anti-inflammatory and antioxidant properties. Genipin, however, is unstable under physiological conditions, and *Lc*S contributes to its stabilization.[54]

Yan,[55] induced acute liver injury in mice and evaluated the effect of *Lc*S on various markers of inflammation, liver damage, and gut microbiota composition. The results showed a decrease in the levels of cytokines such as IL-5, IL-10, and RANTES; a reduction in the overexpression of hepatic inflammatory genes such as Ccl11, Lif, and Il11; as well as a decrease in serum levels of gamma-glutamyl transpeptidase (GGT), a marker of liver damage. Furthermore, *Lc*S treatment reduced the *Firmicutes*/*Bacteroidetes* (F/B) ratio in the gut microbiota, suggesting a favorable modulation of the microbial environment.[55]

An increase in the F/B ratio has been associated with intestinal dysbiosis and a chronic inflammatory state.[56] Studies with other probiotics have shown that a decrease in this ratio correlates with a reduction in proinflammatory cytokines such as IL-6 and TNF-á.[56] Therefore, since a decrease in the F/B ratio was observed in Yan's study,[55] *Lc*S may exert an additional anti-inflammatory effect through this mechanism.

On the other hand, IGFBP-3 has been associated with anti-inflammatory effects, partly due to its ability to inhibit NF-êB transcription.[57] In a mouse model study, Kim et al.,[57] observed that overexpression of IGFBP-3 significantly reduced the expression of proinflammatory cytokines such as cyclooxygenase-2, IL-1â, and TNF-á, in addition to decreasing the generation of reactive oxygen species, which contributed to attenuating colonic inflammation.

These findings are relevant, as they suggest that *Lc*S-induced stimulation of IGFBP-3 expression could represent an additional pathway by which it exerts its anti-inflammatory effects.

Effects of *Lc*S on Biomarkers of Inflammation in vivo in Human Models

Research on the effects of *Lc*S in human models is limited. Study populations range from

healthy individuals and athletes to individuals with underlying medical conditions.

Vaisberg et al.,[52] investigated the effects of *Lc*S in marathon runners, obtaining good results on the *Lc*S effect and inflammatory markers. They compared parameters before and after a marathon, resulting from the analysis of nasal mucosa samples and serum inflammatory markers. They identified an increase in proinflammatory cytokines in both the mucosa and serum in the group without *Lc*S. Meanwhile, in the upper airways, the administration of *Lc*S significantly reduced the concentrations of IL-1â, IL-5, IL-6, and IL-13, while increasing IL-10 levels. In addition, a lower infiltration of neutrophils in the nasal mucosa was observed. Likewise, in systemic circulation, the treatment was associated with a decrease in TNF-á and an increase in IL-6 and IL-10.

In healthy adults, Harbige et al.,[50] evaluated the administration of *Lc*S for a prolonged period, having discrete results. The administration consisted of three phases: 4 weeks of administration (priming), followed by 6 weeks without treatment, and, finally, another 4 weeks of supplementation (boost). When evaluating CD14+ monocytes ex vivo (both stimulated with LPS and under basal conditions) a significant decrease in TNF-á levels was observed, as well as a reduction in IL-12 in both groups. Additionally, a decrease in intracellular IL-4 was reported.

However, results in populations with underlying pathologies have been variable. In HIV patients on antiretroviral therapy, Falasca et al.,[49] reported that four weeks of *Lc*S supplementation did not significantly modify systemic inflammatory markers, except for a reduction in serum IL-23. However, at the transcriptional level in PBMNC, notable changes were observed, including decreased mRNA expression of TGF-â and IL-12, along with increased IL-4.

In the context of liver cirrhosis, where intestinal dysbiosis and endotoxemia play a key pathophysiological role,[58] Macnaughtan et al.,[53] found that six months of treatment with *Lc*S did not cause significant changes in the plasmatic levels of proinflammatory (IL-1â, IL-6, IL-8, TNF-á) or anti-inflammatory (IL-10) cytokines.

Clinical evidence suggests that the consumption of foods or supplements based on probiotics modifies the microbiota, with beneficial effects, which are manifested in clinical, anthropometric and biochemical components of metabolic syndrome (MS) in the adult population. Rivero and Monroy[58] analyzed the impact of probiotic supplementation in the prevention or treatment of MS in the adult population, reporting that in 10 randomized clinical studies with 610 participants, no significant differences were found in insulin resistance, obesity (body mass index), atherogenic dyslipidemia or systemic blood pressure; they concluded that the limitations in the reviewed studies imply the need for future lines of research including nutritional treatment or dietary control.

Based on these human studies, it is possible to hypothesize that *Lc*S has better effects on inflammatory markers when administered to healthy individuals; however, the evidence is scarce, so such data should be treated with caution.

CONCLUSION

In recent years, significant progress has been made in research on the association between probiotic consumption and its associated health benefits. For example, they have been proposed as a reliable tool for modulating the intestinal microbiota and a potential therapy for specific disorders or diseases.

In this regard, research on the use of *Lactobacillus casei* Shirota has gained significant interest in recent decades, with a wide variety of studies conducted in cellular, murine, and human models. In general, it has been observed that the best results on inflammatory markers occur with the consumption of *Lc*S in conjunction with other substances such as prebiotics in cellular and murine models; while in human models, the best results are obtained in studies with healthy subjects.

In view of the above, an area of opportunity arises for the clinical use of *Lc*S together with other substances for the reduction of inflammatory markers, given that this strategy provides better results in cellular and murine models, and to date, there are no human studies with this type of intervention.

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This research does not involve any clinical trials.

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Not applicable.

Author contributions

Nicolás Padilla-Raygoza: Conceptualization, make search on literature in electronic database; selected the articles for review for other authors; Rebeca Monroy-Torres: Reviewed the manuscript critically and make some comments; Omar López-Guzmán: Reviewed the articles for quality and if they can be used for this issue; Yaret Valeria Rodríguez-Aguilar: Extract information of articles and generated the table with the results of the all articles.

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