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Review

Is Probiotics Supplementation an Appropriate Strategy to Modulate Inflammation in Physically Active Healthy Adults or Athletes? A Systematic Review

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Abstract: Supplementation with probiotics in sports is on the rise with the aim of improving health and athletic performance. Since intense exercise-induced muscle damage leads to an inflammatory process by increasing circulating inflammatory cytokines, probiotic supplementation may modulate and correct the inflammation. We systematically reviewed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the Scopus, Web of Science, and Medline databases for the 10 years until January 2023. This review aimed to evaluate probiotic supplementation as a strategy for modulating inflammation in healthy physically active adults or athletes. Studies were indexed to assess the effect of probiotic supplementation on cytokine behavior in the inflammatory response in physically active individuals. Of the 136 studies identified in the search, 13 met the inclusion criteria, and their quality was assessed using the McMaster Critical Review Form. The results of these trials indicated a significant improvement in inflammatory cytokines in probiotic-supplemented participants, with a significant increase in anti-inflammatory cytokines (IL-10) and a significant decrease in proinflammatory cytokines (IL-6, TNF-α, and IL-8). This would create uncertainty about probiotics' effect on interleukins' behavior after exercise, and further clinical trials are needed to establish a solid basis.

Keywords: sport supplementation; probiotics; physical activity; athletes; cytokines; inflammation-related biomarkers

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1. Introduction

The human microbiota is a set of microorganisms (bacteria, fungi, archaea, viruses, and parasites) that live in our body and can be differentiated into commensals, mutualists, and pathogens [1]. There are several microbial ecosystems in the human body, the most complex, diverse, and numerous of which are found in the gastrointestinal tract (GIT). The microbiota is specific to each individual and conditioned by their genotype, early exposure to microorganisms in their environment, diet, lifestyle changes, use of antibiotics, and quantity/quality of physical activity [2,3]. In total, the GIT in adults may harbor between 500 and 1000 species of microorganisms, the majority of which are bacteria belonging to the phyla *Bacteroidetes* (25%) and *Firmicutes* (60%), and to a lesser extent *Proteobacteria*, *Verrucomicrobia*, *Fusobacteria*, *Cyanobacteria*, *Actinobacteria* and *Spirochaetes*, *archaea*, *fungi*, *protozoa*, and *viruses*, among many others [4]. It has been described that the *Firmicutes/Bacteroidetes* (F/B)

ratio is key to the homeostatic modulation of GIT. In this sense, increased F/B (obesity) or decreased F/B (inflammatory bowel disease) induce states of dysbiosis [5]. Additionally, a low amount of *Proteobacteria* together with a high presence of *Bacteroidetes*, *Prevotella*, and *Ruminoccus* is favorable for health [4].

Exercise induces physiological responses in the body that attempt to modulate the homeostatic adaptive processes, leading to recovery and tissue remodeling [6]. However, they do not always succeed, leading to metabolic, hormonal, neuro-physical, and immunological changes due to local muscle and systemic inflammatory hyper-responses to strenuous exercise, which is associated with reduced sports performance, increased fatigue, and the establishment of overtraining, putting the health of the athlete at risk [7,8]. In exercise-induced muscle damage (EIMD), an inflammatory process takes place as a consequence of the initial phase of mechanical muscle damage [9], with the release of interleukins (ILs) occurring, mainly IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and macrophage inflammatory protein-1 (MIP-1), which enhance the inflammatory process [10,11]. To this inflammatory response must be added the inflammation caused by oxidative/metabolic stress that occurs during prolonged endurance exercise [9]. Exercise has an intensity- and/or time-dependent effect on the gut microbiota that is independent of the diet consumed [3]. Indeed, the behavior of the microbiota, which acts like an endocrine gland, inducing multifactorial changes in organ function, metabolism, immunity, and host behavior [12]. Regular physical activity and low/moderate-intensity exercise are beneficial adaptations and improve the long-term resistance of the intestinal barrier by reducing the response of heat shock proteins to heat stress by preventing the breakdown of tight junction proteins between the epithelial cells [12], such as those produced by therapeutic exercise in patients with inflammatory bowel disease [13]. However, high-intensity and long-duration exercise causes gastrointestinal disorders known as "exercise-induced gastrointestinal syndrome", by damaging epithelial cells in the gut [14]. It is likely that the competition between muscle and intestinal blood flow, which is resolved in favor of the former during vigorous exercise, causes cell death of the lining epithelium, altering permeability, which facilitates endotoxemia, and triggers immune/inflammatory responses leading to EIMD inflammation [15,16].

The dysregulation of the inflammatory response needs to be modulated to optimize athletic performance and maintain the health of athletes. To this end, sports supplements have been used as a supplement to the athlete's diet [17]. Thus, interest in probiotics as a sports nutritional supplement has grown exponentially in recent years. Probiotics are a class of dietary supplements consisting of *"live microorganisms that, when administered in adequate amounts, confer a health benefit to the host"* [18]. Probiotics may indirectly benefit athletic performance and health status by maintaining gastrointestinal function and health, reducing susceptibility to disease, and modulating host immune expression [16]. The ability of probiotics to improve an individual's immunity is exerted by controlling the communication between immune and inflammatory cells, through the modulation of ILs, as probiotics bind to the membrane receptors of enterocytes, which critically influences the regulation (activation/inhibition) of ILs [16,19]. There are several pharmaceutical forms of probiotic microorganisms available. Commonly used probiotic strains belong to the genera *Lactobacillus*, *Bifidobacterium*, *E. coli Nissle 1917* and *Saccharomyces boulardii* [20]. However, it may not necessarily provide the same health-promoting properties [16]. Furthermore, if a benefit is attributed to one strain, it cannot be extrapolated to other strains of the same species. Some strains of the *Lactobacillus genus (paracasei CNCM I-4034; rhamnosus CNCM I-4036)* and *Bifidobacterium breve (CNCM I-4035)* have anti-inflammatory effects [21].

In summary, there are many reasons to believe that probiotic supplementation can be used as a strategy to interfere with EIMD and/or microbiome inflammatory pathways, but its impact on EIMD-induced ILs remains to be established. Moht et al. [22] described the inflammatory effect in a population of healthy non-athlete adults and in a limited number of cytokines. Quero Calero et al. [23] also reported the effects of probiotics, prebiotics and/or symbiotics in athletes and active individuals, including their effects on

the immune system, oxidative stress, gastrointestinal and respiratory symptoms, but not on EIMD-derived inflammatory cytokines. In 2022, Guo et al. [24] described probiotic supplementation on immune and inflammatory markers in athletes; however, they did not include some inflammatory (IL-15, IL-1alpha, IL-1RAa) or anti-inflammatory (INF-γ) cytokines. These investigators [24] did not describe or discuss in sufficient depth the posology or composition of probiotic supplementation. These authors included athletes in parallel controlled trials exclusively. Therefore, this review critically assesses the effects of probiotic supplementation in physically active adults to analyze the impact of probiotics on the behavior of interleukins in the inflammatory response and anti-inflammatory response in physically active adults and athletes, with a special interest in the composition and posology of supplemented probiotics with different clinical trial designs.

2. Methods

We formulated the research question using the PICOS model according to the standard methods proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]: (i) P (population): healthy, physically active or athletes adults without chronic diseases; (ii) I (intervention): supplementation with probiotics only (understood as live microorganisms); (iii) C (comparison): placebo/control group or pre/post comparison data group; (iv) O (outcomes): markers of inflammation: anti-inflammatory interleukins (IL-1Ra, IL-4, INF-γ, and IL-10) and pro-inflammatory interleukins (IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-15), and TNF-α; (v) S (study design): randomized, double-blind, placebo-controlled, crossover study.

2.1. Search Strategy

The SCOPUS, Web of Science (WOS), and Medline (PubMed) databases were searched for trials from the last 10 years of the database, up until January 2023. The search strategy included terms related to probiotics and the different outcome biomarkers, as well as a combination of these using the Medical Subject Headings (MeSH) index and Boolean operators: (probiotics OR probiotic-bacterium) AND (exercise OR athletes OR sport or physical activity) AND (inflammatory OR immune system OR cytokines OR biomarkers). All trials were included in an Excel spreadsheet to identify possible duplicates.

2.2. Selection Criteria

The following inclusion criteria were applied for the final selection of trials: (a) healthy adults without chronic diseases, physically active (excluding animal/in vitro studies); (b) studies evaluating probiotic supplementation alone (excluding any combination with any other supplements or prebiotics); (c) clinical trials, randomized or not, placebo/control group or of pre/post comparison (excluding systematic reviews, meta-analyses, popular articles, letters to the editor or opinion articles and any other non- original studies); (d) measured variables (primary or secondary) that were biomarkers of inflammation: anti-inflammatory interleukins (IL-1Ra, IL-4, INF-γ, and IL-10) and pro-inflammatory interleukins (IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-15), and TNF-α; and (e) trials with clear information on dosage and duration of probiotic supplementation (understood as live microorganisms). All records that did not meet these criteria were excluded.

2.3. Quality Assessment

The methodological quality of studies was assessed using the McMaster University Occupational Therapy Evidence-Based Practice Research Group [26] as a critical appraisal tool. These guidelines are suitable for the assessment of randomized and non-randomized studies because they are a comprehensive and reliable tool for assessing the methodological quality of quantitative evidence.

3. Results

3.1. Study Selection

The literature search yielded 142 studies, of which 136 studies were retrieved from the electronic databases WOS, SCOPUS, and PubMed, and six studies were retrieved from other sources, such as ResearchGate and reference lists of relevant studies. After the exclusion of 16 duplicates, we examined a total of 120 identified articles from databases were retrieved. After title and abstract assessment, 40 articles were considered as potential studies. After full-text review and assessment of potential registries, 13 studies [27–39] were included in the systematic review (Figure 1).

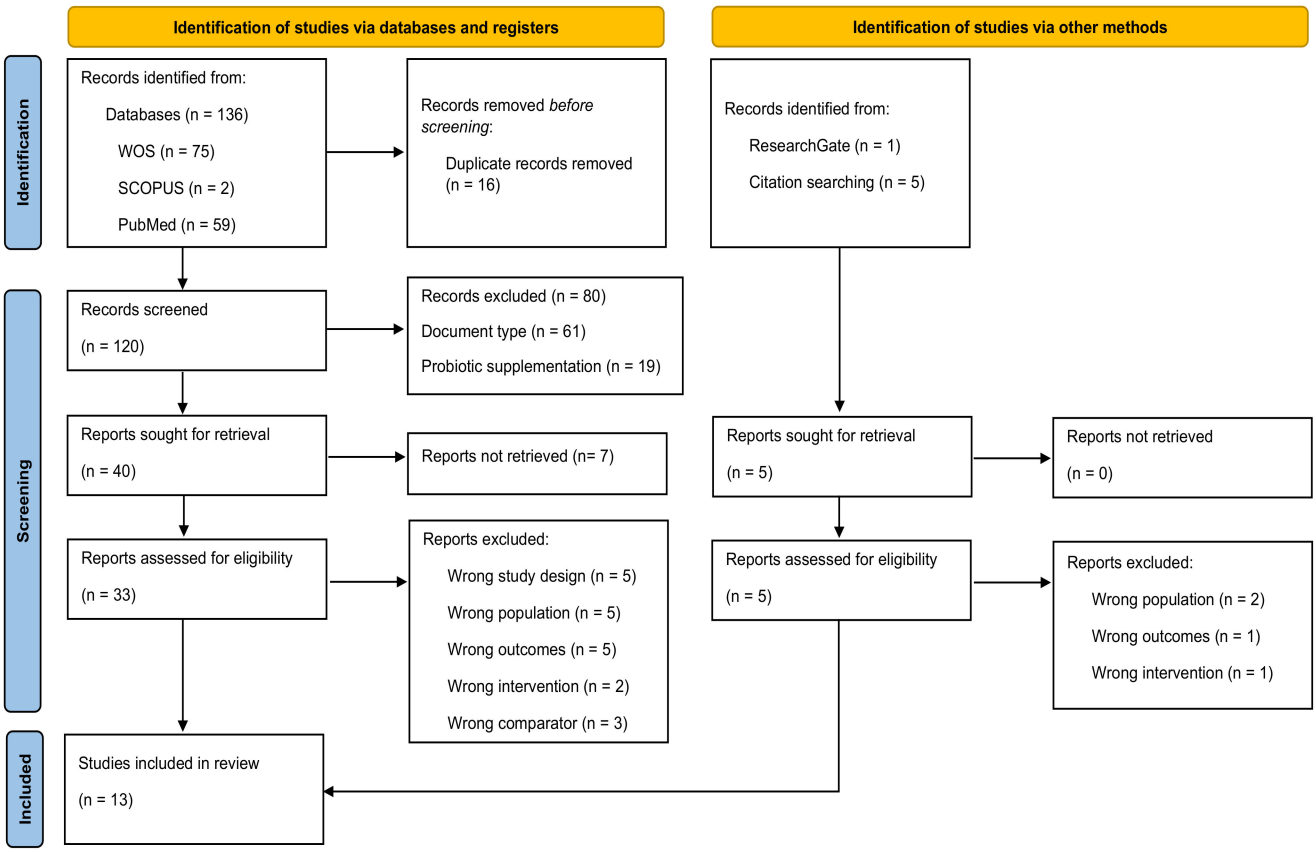

Figure 1. Flow diagram depicting the identification and selection processes of relevant studies according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

3.2. Quality Assessment

Four studies [27,28,30,39] had results $\geq$ 15 points, corresponding to "excellent" quality, and nine [29,31–38] studies had results between 13 and 14 points, corresponding to "very good" quality (Table 1).

Table 1. Results of the methodological quality assessment of included studies—McMaster Critical Review Form for Quantitative Studies [26].

Study	Item																Total	%	Quality Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16			
Axelrod et al., 2019 [27]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	15	93.8	E
Batatinha et al., 2020 [28]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	100	E
Gill et al., 2016 [32]	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	13	81.25	VG
Hoffman et al., 2019 [33]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	14	87.5	VG
Huang et al., 2019 [34]	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	0	13	81.25	VG
Jager et al., 2016 [35]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	14	87.5	VG
Lamprecht et al., 2021 [36]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	14	87.5	VG
Pugh et al., 2019 [37]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	14	87.5	VG
Pugh et al., 2020 [38]	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	14	87.5	VG
Schreiber et al., 2021 [39]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	16	100	E
Shing et al., 2014 [29]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	14	87.5	VG
Tavares-Silva et al., 2021 [30]	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	16	100	E
Vaisberg et al., 2019 [31]	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	14	87.5	VG

Abbreviations: 0 = not fulfilled criterion; 1 = fulfilled criterion; E = excellent; VG = very good; item 1: study purpose; item 2: literature review; item 3: study design; item 4: blinding; item 5: sample description; item 6: sample size; item 7: ethics and consent; item 8: validity of outcomes; item 9: reliability of outcomes; item 10: intervention description; item 11: statistical significance; item 12: statistical analysis; item 13: clinical importance; item 14: conclusions; item 15: clinical implications; item 16: study limitations.

3.3. Characteristics of the Participants and the Intervention

The total number of physically active adults included in this systematic review was 300 (248 men, 4 women, and 48 unspecified). A total of 269 participants were endurance athletes [22–27,29,31–34], 27 were elite athletes [39], and 31 participants were strength athletes [33,35]. Six studies used a supplement manufactured for the study [22,25,26,29,30,34], six studies used a proprietary commercial supplement [29,32,33,36–38], and one study did not report [28]. Regarding the strains used, eight studies [28–30,35–39] used mixed strains, and five studies used single strains [27,31–34]. The doses of probiotics used ranged from 0.25×10^8 Colony Forming Units (CFU) to $250{,}000 \times 10^8$ CFU. The timing of probiotic supplementation was: two trials [33,37] after breakfast, one trial [38] post-exercise, one trial [28] after dinner, and three trials [32,34,36] twice a day and six trials [27,29–31,35,39] once a day without specifying the exact time of the supplementation. The duration of the intervention ranged from 1 week [32] to 14 weeks [36]. The pharmaceutical form used for probiotics supplementation was: capsules [27,29,30,34,35,37–39], powder [28,33,36], and drinks [31,32] (Table 2).

Table 2. Characteristics of participants and supplementation protocols of the selected studies.

Characteristics	Types	Study
Participants	Endurance training	[27–32,34,36–39]
	Strength training	[33,35]
Supplementation product	Manufactured	[27,30,31,34,35,39]
	Registered product®	[29,32,33,36–38]
	Not reported	[28]
Strain formulation	Single	[27,31–34]
	Mixed	[28–30,35–39]
Total dose (10^8 CFU) × day^{-1}	0–50 Low dose	[27,30,33,36,37]
	51–500 Medium dose	[28,29,31,34,35]
	>501 High dose	[32,38,39]
Duration	1 week	[32]
	2 weeks	[33]
	3 weeks	[35]
	4 weeks	[27,29,34,37,38]
	30 days	[28,30,31]
	90 days	[39]
	14 weeks	[36]
Dose schedule	After breakfast	[33,37]
	Post-exercise	[38]
	After dinner	[28]
	Twice daily	[32,34,36]
	Once a day	[27,29–31,35,39]
Pharmaceutical form	Capsules	[27,29,30,34,35,37–39]
	Powdered	[28,33,36]
	Drink	[31,32]

Abbreviations: a.m. = ante meridiem; p.m. = post meridiem; CFU = colony forming unit.

3.4. Outcome Measures

Table 3 summarizes the content of the studies included in this systematic review. It includes information on the author(s), year of publication, country, the sample studied, level of sports, gender, number, age, height, weight, body mass index, and maximum volume of oxygen uptake (VO_2max) of the participants. The study design includes the control group if the study included one; the supplementation protocol, which specifies the type of probiotics used, the dose, and time of administration; the interleukins analyzed; the main effects; and finally, the results.

Table 3. Studies included in the systematic review of the effect of Probiotics supplementation on interleukin response in healthy adults.

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Axelrod et al., 2019, USA [27]	Randomized, double-blind, placebo-controlled crossover trial	7 endurance athletes Age (mean ± SD): 31 ± 2.3 y BMI (mean ± SD): 24.3 ± 3.4 kg/m^2 Body Fat (mean ± SD): 20.1 ± 5.9% VO_2max (mean ± SD): 57.9 ± 4.5 mL/kg/min No withdrawals reported	2×10^8 CFU 1 capsule (200 mg)/day Lactobacillus salivarius UCC118 4 weeks	IL-6	IG vs. CG ↓IL-6 IG: Change from baseline ↓IL-6
Batatinha et al., 2020 Brazil [28]	Randomized, double-blind, placebo-controlled trial	40 ♂marathon athletes Age (mean ± SD) IG: 35.9 ± 5.8 y CG: 40.4 ± 7.8 y Weight (mean ± SD) IG: 79.3 ± 10.9 kg CG: 72.6 ± 10.2 kg Height (mean ± SD) IG: 1.75 ± 0.06 m CG: 1.75 ± 0.09 m Fat mass (mean ± SD) IG: 16.9 ± 5.8% CG: 11.32 ± 4.4% 13 withdrawals/lost to follow-up 27 participants completed the study 13 participants CG 14 participants IG	Bifidobacterium animalis subsp. Lactis 10×10^9 CFU + Lactobacillus acidophilus 10×10^9 CFU Powdered Sachets dissolved in water before sleeping 30 days	IL-1β IL-2 IL-4 IL-6 IL-8 IL-10 IL-15 TNF-α INF-γ	IG: Change from baseline ↓IL-1β ↓IL-2 ↑IL-4 ↑IL-6 ↑IL-8 ↑IL-10 ↓IL-15 ↑TNF-α ↓INF-γ

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Gill et al., 2016. United Kingdom [32]	Randomized, double-blind, placebo-controlled crossover trial	8 ♂endurance athletes (triathlon, road, trail running, ultra-endurance running) Age (mean ± SD): 26 ± 6 y Nude body mass (mean ± SD): 70.2 ± 8.8 kg Height (mean ± SD): 1.75 ± 0.05 m VO_2max (mean ± SD): 59 ± 5 mL/kg/min No withdrawals reported	1×10^{11} CFU of *Lactobacillus casei.* Drink 500 mL in the morning (8:00–9:00 a.m.) and Drink 500 mL in the afternoon (4:00–5:00 p.m.) 7 days	IL-1β IL-6 IL-8 IL-10 TNF-α INF-γ	GI vs. CG ↔IL-1β ↔IL-6 ↔IL-8 ↔IL-10 ↑TNF-α ↔INF-γ IG: Change from baseline ↑IL-1β *↑IL-6 *↑IL-8 *↑IL-10 *↑TNF-α ↔INF-γ
Hoffman et al., 2019, Israel [33]	Randomized, double-blind, placebo-controlled trial	16 ♂soldiers in combat training Age (mean ± SD) IG: 20.0 ± 0.6 y CG: 20.2 ± 0.6 y Weight (mean ± SD) IG: 72.0 ± 6.5 kg CG: 76.1 ± 8.2 kg Height (mean ± SD) IG: 1.76 ± 0.063 m CG: 1.80 ± 0.096 m 1 withdrawals/lost to follow-up 15 participants completed the study 7 participants CG 8 participants IG	1×10^{9} CFU Inactivated Bacillus coagulans. Powdered Sachets dissolved in 250 mL of water 14 days	IL-1β IL-6 IL-8 IL-10 TNF-α INF-γ	GI vs. CG ↔IL-1β ↔IL-6 ↔IL-8 ↔IL-10 ↔TNF-α ↔INF-γ IG: Change from baseline ↑IL-1β ↓IL-6 ↓IL-8 ↑IL-10 ↓TNF-α ↔INF-γ

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Huang et al., 2019 Taiwan [34]	Randomized, double-blind controlled trial	18 triathletes Age (median ± SEM) IG: 20.2 ± 0.67 y CG: 21.1 ± 1.5 y Weight (mean ± SD) IG: 63.5 ± 8.5 kg CG: 64.8 ± 5.7 kg Height (mean ± SEM) IG: 168 ± 0.08 m CG: 1.71 ± 0.05 m BMI (mean ± SEM): IG: 22.5 ± 1.2 kg/m^2 CG: 22.1 ± 1.3 kg/m^2 No withdrawals reported CG: 9 participants IG: 9 participants	3×10^{10} CFU 2 capsules/day L- Plantarum PS128 4 weeks	IL-4 IL-6 IL-8 IL-10 TNF-α INF-γ	GI vs. CG ↓IL-4 *↓IL-6 *↓IL-8 ↓IL-10 *↓TNF-α *↑INF-γ IG: Change from baseline *↑IL-4 ↑IL-6 ↔IL-8 *↑IL-10 ↑TNF-α ↑INF-γ
Jäger et al., 2016 USA [35]	Randomized, double-blind, placebo-controlled trial	15 ♂healthy strength training Age (median ± SD): 25 ± 4 y Weight (mean ± SD): 81.1 ± 10.3 kg Height (mean ± SD): 1.77 ± 0.08 m No withdrawals reported	1×10^{10} CFU S. thermophilus FP4 & B. brevis BR03 Capsules 21 days	IL-6	GI vs. CG ↓IL-6 IG: Change from baseline ↔IL-6

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Lamprecht et al., 2012 Austria [36]	Randomized, double-blind, placebo-controlled trial	24 ♂resistance trained (triathlon, running, cyclists) Age (median ± SD) IG: 37.6 ± 4.7 y CG: 38.2 ± 4.4 y Weight (mean ± SD) IG: 80.2 ± 7.9 kg CG: 81.6 ± 6.3 kg BMI (mean ± SD): IG: 23.7 ± 2.2 kg/m^2 CG: 23.9 ± 3.1 kg/m^2 VO_2max (mean ± SD): IG: 51.2 ± 4.1 mL/kg/min CG: 50.3 ± 3.6 mL/kg/min 1 withdrawals/lost to follow-up 23 participants completed the study 12 participants CG 11 participants IG	10×10^{10} CFU Powdered Sachets mix: -Bifidobacterium bifidum CU23 -Bifidobacterium lactis CU51 -Lactobacillus brevis CU63 -Enterococcus faecium CU54 -Lactobacillus acidophilus CU22 -Lactococcus lactis CU58 14 weeks	IL-6 TNF-α	GI vs. CG ↔IL-6 ↓TNF-α IG: Change from baseline *↑IL-6 ↑TNF-α

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Pugh et al., 2019 United Kingdom [37]	Randomized, double-blind controlled trial	24 runners (20 ♂; 4♀) Age (median ± SD) IG: 34.8 ± 6.9 y CG: 36.1 ± 7.5 y Height (mean ± SD) IG: 1.79 ± 0.06 m CG: 1.75 ± 0.11 m Body mass (mean ± SD) IG: 76.5 ± 9.4 kg CG: 73.5 ± 11.3 kg VO_2max (mean ± SD) IG: 57.6 ± 8.0 mL/kg/min CG: 56.4 ± 8.6 mL/kg/min 4 withdrawals/lost to follow-up 23 participants completed the study 9 participants CG 11 participants IG	2.5×10^{10} CFU 1 capsule/day -Lactobacillus acidophilus CUL60 -L. acidophilus CUL21 -Bifidobacterium bifidum CUL20 -Bifidobacterium animalis subsp lactis CUL34 28 days	IL-6 IL-8 IL-10	GI vs. CG ↔IL-6 ↔IL-8 ↔IL-10 IG: Change from baseline *↑IL-6 *↑IL-8 *↑IL-10
Pugh et al., 2020 United Kingdom [38]	Randomized, double-blind, placebo-controlled trial	7 trained cyclists Age (median ± SD): 23.4 ± 4.0 y Body mass (mean ± SD): 73.4 ± 7.1 kg VO_2max (mean ± SD): 64.0 ± 2.2 mL/kg/min	2.5×10^{13} CFU 1 capsule/day -Lactobacillus acidophilus CUL60 -Lactobacillus acidophilus CUL21 -Bifidobacterium bifidum CUL20 -Bifidobacterium animalis subsp lactis CUL34 28 days	IL-1α IL-6 IL-8 IL-10	GI vs. CG ↓IL-1α ↓*IL-6 ↓IL -8 ↑IL -10 IG: Change from baseline ↑IL-1α ↑IL-6 ↑IL-8 ↑IL-10

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Schreiber et al., 2021 Israel [39]	Randomized, double-blind, placebo-controlled crossover trial	27 ♂elite cyclists Age (median ± SD) IG: 25.9 ± 4.6 y CG: 29.5 ± 6.2 y Height (mean ± SD) IG: 1.78 ± 0.05 m CG: 1.75 ± 0.04 m Weight (mean ± SD) IG: 71.3 ± 8.9 kg CG: 72.0 ± 6.2 kg BMI (mean ± SD) IG: 22.6 ± 2.7 kg/m^2 CG: 23.5 ± 1.9 kg/m^2 VO_2max (mean ± SD) IG: 66.9 ± 6.4 mL/kg/min CG: 63.2 ± 5.0 mL/kg/min No withdrawals reported 16 participants CG 11 participants IG	1.5×10^{10} CFU 1 capsule/day -Lactobacillus Helveticus Lafti L10 -Bifidobacterium animalis Lafti B94 -Enterococcus Faecium R0026 -Bifidobacterium Longum R0175 -Bacillus Subtilis R0179 90 days	IL-6 TNF-α	GI vs. CG ↔IL-6 ↔TNF-α IG: Change from baseline ↑IL-6 ↓TNF-α

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Shing et al., 2013 Australia [29]	Double-blind, placebo-controlled cross-over trial	10 ♂trained runners Age (median ± SE): 27 ± 2 y CG: 29.5 ± 6.2 y Height (mean ± SE): 1.77 ± 0.02 m Body mass (mean ± SE): 71.5 ± 2.3 kg VO_2max (mean ± SD) 62.6 ± 2.1 mL/kg/min No withdrawals reported	4.5×10^{10} CFU 1 capsule/day -*Lactobacillus acidophilus* -*L. rhamnosus* -*L. casey* -*B. brevis* -Streptococcus thermophilus -*L. plantarum* -*L. fermentum* -*Bifidobacterium lactis* -*B. bifidus* 4 weeks	IL-1Ra IL-6 IL-10 TNF-α	GI vs. CG ↓IL-1Ra *↓IL-6 *↓IL-10 *↓TNF-α IG: Change from baseline ↑IL-1Ra ↑IL-6 ↑IL-10 ↑TNF-α
Tavares-Silva et al., 2021 Brazil [30]	Randomized, double-blind, placebo-controlled trial	14 ♂marathon runners Age (median ± SD) IG: 41.57 ± 3.20 y CG: 38.28 ± 3.09 y Height (mean ± SD) IG: 1.75 ± 0.030 m CG: 1.79 ± 0.052 m BMI (mean ± SD) IG: 23.08 ± 1.83 kg/m^2 CG: 24.90 ± 1.81 kg/m^2 VO_2max (mean ± SD) IG: 56.92 ± 8.35 mL/kg/min CG: 54.53 ± 6.88 mL/kg/min No withdrawals reported 7 participants CG 7 participants IG	5×10^9 CFU 2 g/day Capsules -*Lactobacillus acidophilus* LBG80 -*Lactobacillus paracasei* LPCG110 -Lactobacillus subp. lactis LLL-G25 -*Bifidobacterium* animalis subp lactis BL-G101 -*Bifidobacterium bifidum* BB-G90 90 days	IL-1β IL-2 IL-4 IL-6 IL-10 TNF-α	GI vs. CG ↔IL-1β ↔IL-2 ↔IL-4 ↔IL-6 *↑IL-10 ↔TNF-α IG: Change from baseline ↑IL-1β ↓IL-2 ↓IL-4 ↑IL-6 ↑IL-10 ↓TNF-α

Table 3. *Cont.*

First Author, Year of Publication, and Country	Study Design	Participants (Baseline Sample Size and Characteristics, Withdrawals, and Final Group Sample Size)	Intervention	Outcomes	Results
Vaisbegr et al., 2019 Brazil [31]	Randomized, double-blind, placebo-controlled trial	42 ♂amateur marathoners Age (median ± SD) IG: 39.6 ± 8.8 y CG: 40.1 ± 10.3 y Height (mean ± SD) IG: 1.73 ± 0.06 m CG: 1.77 ± 0.07 m Weight (mean ± SD) IG: 72.4 ± 7.8 kg CG: 76.5 ± 10.4 kg BMI (mean ± SD) IG: 23.4 ± 2.4 kg/m^2 CG: 24.4 ± 2.2 kg/m^2 Body fat (mean ± SD) IG: 16.5 ± 6.6% CG: 18.6 ± 7.5% VO_2max (mean ± SD) IG: 57.86 ± 6.85 mL/kg/min CG: 57.64 ± 6.89 mL/kg/min 14 withdrawals/lost to follow-up 42 participants completed the study 22 participants CG 20 participants IG	40×10^9 CFU Drink (80 g) fermented milk 1 bottle/day *Lactobacillus casei* shirota (Lcs) 30 days	IL-1β IL-1Ra IL-4 IL-6 IL-10 TNF-α	<u>GI vs. CG</u> ↔IL-1β ↔IL-1Ra ↔IL-4 ↔IL-6 *↑IL-10 ↔TNF-α <u>IG: Change from baseline</u> *↑IL-1β ↓IL-1Ra ↑IL-4 *↑IL-6 *↑IL-10 *↑TNF-α

Abbreviations: ↑ = no significant increase; ↓ = no significant decrease; ↔ = no significant change. *↑ = significant increase; *↓ = significant decrease; CG = control group; IG = intervention group; SD = standard deviation; SEM = standard error of the mean; SE = standard error; IL = interleukin; TNF-α = tumor necrosis factor-alpha; INF-γ = interferon-gamma; CFU = colony forming units; kg = kilograms; m^2 = square meters; % = percentage; BMI = body mass index; ♂= men; ♀= women; mg = milligrams; m = meters; y = years; a.m. = ante meridiem ; p.m. = post meridiem; mL = milliliters; min = minutes; VO_2max = volume maximum oxygen.

3.5. Anti-Inflammatory Cytokines

Significant increases ($p < 0.05$) in IL-10 (anti-inflammatory) have been observed in the control group [30,31] and at baseline [32,34,37], contrasting with significant decreases ($p < 0.05$) in IL-10 observed in trained runners [29]. Only one study reported a significant increase ($p < 0.05$) in IL-4 [34] in the intervention group compared to the baseline. Shing et al. [29] described a favorable trend of increased IL-1Ra in the intervention group after 4 weeks of supplementation with a probiotics mixture of 4.5×10^{10} CFU (Table 3). Huang et al. [34] reported a significant increase ($p < 0.05$) in INF-γ in the supplemented group compared to the control group. Two studies [32,33] showed no change when comparing both conditions (intervention and control).

3.6. Pro-Inflammatory Cytokines

The major pro-inflammatory cytokines TNF-α [28–34,36,39], IL-6 [27–39], IL-1α [38], IL-1β [28,30–33] and IL-8 [28,32–34,37,38] were evaluated as markers of exercise inflammation in the studies included in this systematic review (Table 3).

Pugh et al. [38] showed a substantial, non-significant decrease ($p > 0.05$) for IL-1α in seven supplemented elite cyclists compared to the control group; however, a trend towards an increase was observed in the group supplemented with a probiotics mixture (2.5×10^{13} CFU) compared to baseline [38]. In four studies [30–33], no changes in IL-1β were observed in supplemented groups compared to control groups (Table 3).

For IL-6, three trials [29,34,38] reported significant reductions ($p < 0.05$) in the probiotic group compared with the non-supplemented group. In 7 of the studies [30–33,36,37,39] included in this systematic review, no changes were observed in the intervention group compared to the control group, although 4 studies [31,32,36,37] reported significant increases ($p < 0.05$) in IL-6 throughout the study in adults supplemented with probiotics (Table 3).

Only the study by Huang et al. [34] in triathletes described a significant decrease ($p < 0.05$) in IL-8 in the supplemented group with *L-Plantarum* PS128 (3×10^{10} CFU) compared to the control group, although significant increases ($p < 0.05$) in IL-8 have been observed in physically active adults following probiotic supplementation [32,37] (Table 3).

Significant decreases ($p < 0.05$) in TNF-α were reported in two studies [29,34] included in this review, in triathletes [34] and runners [29] supplemented with 3×10^{10} CFU and 4.5×10^{10} CFU, respectively, compared to the control group. Probiotic supplementation showed no effect on TNF-α compared with the control group in four studies [30,31,33,39] that were included in this systematic review. In addition, significant increases ($p < 0.05$) were found in the supplemented group compared with baseline in endurance athletes (32) and marathoners [31]. Five studies [28,29,33,34,36] included in this systematic review showed a non-significant increase ($p > 0.05$) in TNF-α in the supplemented group at the end of the study compared to the baseline (Table 3).

4. Discussion

This systematic review aimed to analyze the effect of probiotic supplementation on cytokine levels in physically active healthy adults or athletes. Thirteen trials were selected because they met the inclusion and/or exclusion criteria. In general, it is difficult to assess the effect of probiotics on the modulation of exercise-induced inflammation, as it would be influenced by the type/duration of exercise, the amount/type of each probiotic used, and the duration of supplementation. Therefore, there is no clear evidence of consistent beneficial effects of probiotic supplementation on the ability of probiotics to modulate immune and/or inflammatory dysfunction after exercise. The duration of probiotic supplementation varied widely between trials. It is likely that effects on inflammatory markers require several months of supplementation rather than a few weeks. The heterogeneity in the duration of supplementation may also explain the uncertainty in the results. For example, no changes were observed when comparing the two study conditions (intervention and control) [30–33,36,37,39], and significant increases in inflammatory cytokines

occurred in the intervention condition throughout the study [31,32,36–38]. However, there was a significant increase in the anti-inflammatory cytokines, IL-10, [30,31], accompanied by a significant decrease in the pro-inflammatory cytokines, IL-6 [29,34,38], TNF-α [29,34], and IL-8 [34] in the intervention group compared to the control group. In addition, no probiotic-related adverse effects were reported. Therefore, the results of this systematic review have been divided into sections for a more precise analysis.

4.1. Probiotics Supplementation

The trials selected for this review used different strains of probiotics in the supplementation periods: *Lactobacillus salivarius* [27], *Lactococcus lactis* [30,36], *Bacillus coagulans* [33], *Bifidobacterium animalis* [28,30,37–39], *Lactobacillus acidophilus* [28–30,36–38], *Lactobacillus casei* [29,31,32], *Lactobacillus helveticus Lafti* [39], *Enterococcus faecium* [36,39], *Bifidobacterium longum* [39], *Bacillus subtilis* [39], *Lactobacillus lactis* [30], *Bifidobacterium bifidum* [29,30,36–38], *Bifidobacterium breve* [29,35], *Bifidobacterium lactis* [29,36], *Lactobacillus brevis* [36], *L-plantarum* [29,34], *L-rhamnosus* [29], *Streptococcus thermophilus* [29,35] and *L. fermentum* [29]. The efficacy of probiotics depends not only on the type of strain, but also on the dose administered [40]. However, there is no specific/standard dose induces beneficial effects or that generates changes in the physiological homeostasis of the supplemented individuals [41]. The International Olympic Committee (ICO), in 2018, noted moderate support for the use of probiotics in athletes with 1.0×10^{10} CFU per day [42] and oral doses of probiotics have ranged from 10^8 to 10^{10} CFU per day [43], although the doses of probiotics used in this review ranged from 0.25×10^8 to 25×10^{12} CFU [27–39].

It is important to consider the possible risks or side effects that probiotic supplementation may cause. For example, probiotics may be responsible for mild gastrointestinal symptoms such as abdominal pain, nausea, loose stool, and bloating, which disappear within a few days of taking them [44]. In general, probiotic supplementation is safe, but caution should be exercised in people with serious health conditions, such as severe acute pancreatitis, inflammatory bowel disease, liver disease, and human immunodeficiency virus No adverse effects were reported in the 13 trials analyzed in this systematic review [27–39].

4.2. Anti-Inflammatory Cytokines

IL-10 triggers an increased anti-inflammatory response, and is one of the cytokines with the most potent anti-inflammatory action. The increase in IL-10 and IL-1Ra levels after exercise occurred after an increase in plasma IL-6 [45,46], which could justify the increases in IL-10 in the supplemented group in 10 studies [28–34,37,38], and significant in four studies [31,32,34,37], compared to baseline. A significant increase in IL-10 in the control group was also observed in marathon runners [30,31], and a significant increase was observed in elite cyclists [38]. This may suggest that probiotics play an additional role to exercise in the stimulation and release of IL-10 in the face of exacerbated inflammatory responses generated by high-intensity exercise situations [45]. The immunoregulatory effects of probiotics may be due to the action of Treg cells and their ability to increase the synthesis of IL-10 to attenuate excessive inflammatory responses (Figure 2), as occurs in inflammatory bowel disease and some autoimmune diseases [47]. These findings are in contrast to those described in a recent meta-analysis of 5 randomized clinical trials in which healthy athletes supplemented with probiotics showed a significant reductions in IL-10 concentrations compared with the control group [24]. These differences may be due to the magnitude of the global anti-inflammatory effect of probiotics, since by reducing proinflammatory cytokines levels, they no longer stimulate the production of anti-inflammatory cytokines such as IL-10, IL-4, IL-1Ra and INF-γ [18,24].

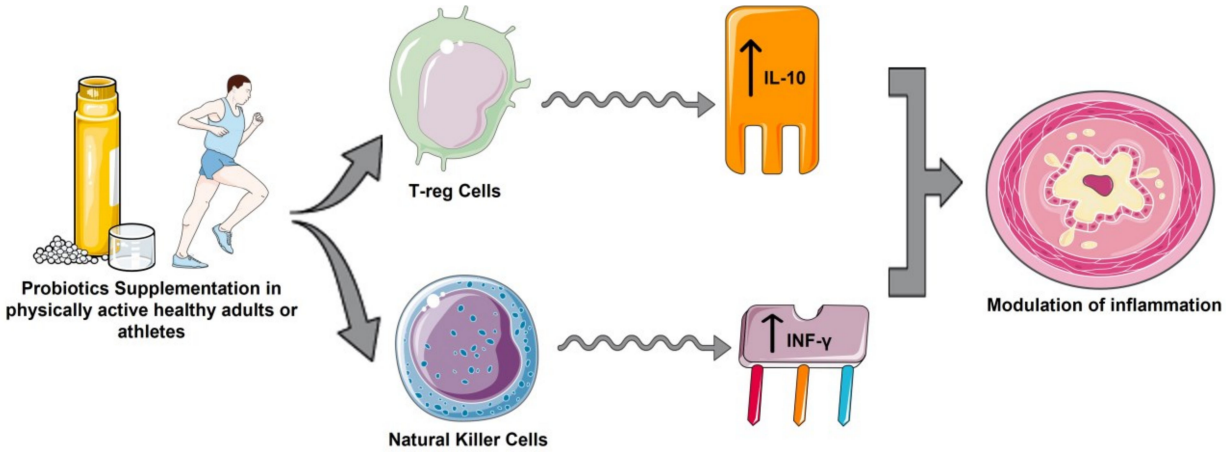

Figure 2. Anti-inflammatory effects of probiotics in physically active healthy adults or athletes. (Created by Authors: Fernández-Lázaro et al. for this study).

In a previous study [24], the group of athletes supplemented with probiotics showed a significant advantage in IFN-γ levels compared to the control group. These results are similar to those described by Huang et al. [34], although Batatinha et al. [28] described a slight downward trend for IFN-γ in marathoners. Probiotics could condition NK cells by interacting with intestinal epithelial cells, inducing an increase in IFN-γ secretion (Figure 2) [47]. In the 13 studies [27–39] included in this review, no significant increase in IL-4 levels was observed compared with the placebo group. This may be a consequence of the adaptation processes of IL-4 to continuous/regular exercise [48].

4.3. Pro-Inflammatory Cytokines

Acute muscle inflammation caused by intense contractions during exercise could lead to leukocyte infiltration and increased levels of inflammatory cytokines such as TNF-α, IL-8, and IL-6. IL-6 is a key member of the cytokine network, and plays a critical role in acute inflammation [10,11]. Thus, pro-inflammatory cytokines were elevated after an exercise in the supplemented group, including TNF-α (31,32), IL-6 (31,32,36,37), IL-8 (32,37), IL-1α [38], and IL-1β [31].

In the results evaluated (Table 3), probiotics significantly reduced the production of the pro-inflammatory cytokines TNF-α [29,34], IL-6 [29,34,38], and IL-8 [34] compared to the control group. The inflammatory power of probiotics may be due to their effect on inflammatory signaling cascades by deregulating intracellular pathways of immune cells mitogen-activated protein kinases (MAPKs) that act on transcription factors: Janus kinase (JAK/STAT), nuclear factor κB pathway (NF-κB), Jun-1, and Fos [47]. The potential inhibition of NF-κB by the action of probiotics would trigger the suppression of the activation and phosphorylation of JAK/STAT proteins and inhibit MAPK signaling through its interaction with three key members of this pathway, including JNK, p38, and ERK [17]. Another possible effect of probiotics is to act on histamine, specifically on the H2 receptors of antigen-presenting cells, leading to a reduction in TNF-α, and MIP-1 [47]. The pathway mediated by probiotics metabolites such as short-chain fatty acids (SCFA), such as propionate, acetate, and butyrate [18], would have anti-inflammatory activity by binding to specific receptors on intestinal epithelial cells and suppressing the production of pro-inflammatory cytokines by the immune cells [47]. For example, it has recently been described that oats could promote the intestinal microbiota through an increased production of SFCA [49]. In this sense, Guo et al. [24] recently showed that probiotic supplementation significantly reduced the level of TNF-α and showed a significant decrease in IL-1β, IL-6, and IL-8. However, only 4/13 studies covered herein were reviewed by Gao et al. [24].

5. Future Scenarios

While it is true that potential benefits to inflammatory response have been described compared to non-supplemented athletes, specifically based on the significant increases in IL-10 [31,32,34,37], and significant decreases in TNF-α [29,34], IL-6 [29,34,38], and IL-8 [34], probiotics were unable to control the inflammatory response after exercise [31,32,36–38]. This would create uncertainty regarding the effect of probiotics on the behavior of cytokines after exercise. Furthermore, it is difficult to specifically recommend single-strain or mixed-strain formulations of probiotics, as the benefits experienced are strain-specific and will depend on the dose and time of supplementation, as well as the duration, intensity, and type of exercise. However, these findings could be encouraging as they would represent an important improvement in supplementation strategies aimed at improving the inflammatory response and therefore exercise performance, although further studies are needed to confirm this. It should be noted that supplementation should always be prescribed on an individual basis and supervised by a specialist.

6. Strengths and Limitations

The authors of this review acknowledge several limitations. Firstly, a limited number of manuscripts met the inclusion criteria, with a total of 13 records, although our systematic approach followed the PRISMA method [25] and the search was conducted using three electronic databases as SCOPUS, WOS, and Medline (PubMed). The McMaster methodological quality assessment tool [26] was used to ensure that all selected records met minimum quality criteria, the high rate of papers excluded for insufficient quality, and a several and a range of outcomes commonly used in sports supplementation research were included. Secondly, the high heterogeneity of the studies in terms of outcomes, supplement dosage, and intervention duration warrants caution in interpreting the results.

7. Conclusions

Overall, the probiotics selected in the studies in this systematic review may have some anti-inflammatory effects by modulating pro-inflammatory cytokines and stimulating anti-inflammatory cytokines. However, further studies are needed to identify probiotic strains that may play a critical role in inflammatory homeostasis, as well as studies to establish approaches to modulate the concentration or composition of probiotics.

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Abbreviations

CFU	Colony Forming Units
EIMD	Exercise-Induced Muscle Damage
GIT	Gastrointestinal Tract
ICO	International Olympic Committee
ILs	Interleukins
JAK	Janus Kinase
MAPKs	Mitogen-Activated Protein Kinases
MeSH	Medical Subject Headings

MIP-1	Macrophage Inflammatory Protein-1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyzes
SCFA	Short-Chain Fatty Acids
TNF-α	Tumor Necrosis Factor-alpha
VO_2max	Maximum Volume of Oxygen
WOS	Web of Science

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