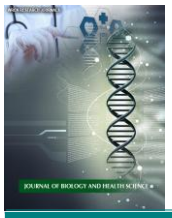

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Research Article

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Antiviral Activity of Probiotics in the Prophylaxis and Treatment of Respiratory Infections Associated with Coronavirus (COVID-19): A Meta-Analysis of Randomized Controlled Trials

Slimane Chawki Mokadem[1*], Mostefa Naimi[1,2] and Omar Alami[1]

[1]Department of Biology, University Centre Nour Bachir of El-Bayadh, El-Bayadh, Algeria

[2] Department of Biology, Djillali Liabes University, Sidi bel-Abbes, Algeria

[*]**Correspondence:** Slimane Chawki Mokadem, Department of Biology, Faculty of Natural Sciences and Life, University Centre Nour Bachir of El-Bayadh, 32000 El-Bayadh, Algeria, E-mail: chawki.mokadem98@gmail.com; DOI: https://doi.org/10.56147/jbhs.1.1.2

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Abstract

Introduction: Probiotics, living microorganisms administered in sufficient quantities, exert beneficial effects on host health. Given the high prevalence of SARS-CoV-2, recent studies suggest potential positive impacts of probiotics on COVID-19 patients.

Methods: A predetermined search strategy encompassing seven databases, NCBI, PubMed, Science Direct, Springer Link, Embase, CNKI and Cochrane Library Databases, was implemented. Human RCTs were scrutinized independently for data extraction, quality and risk of bias assessment and statistical analysis. Pooled data, employing the random-effects model, are expressed as Standardized Mean Differences (SMDs) with 95% Confidence Intervals (CIs). Assessments of the p value and heterogeneity (I^2) were conducted and quantified.

Results: Five studies comprising 282 out of 375 participants were included. The meta-analysis revealed effects on various parameters: CRP level (SMD=0.26 MG/L, 95% CI [0.10, 0.43], p= 0.002, (I^2=67%, p=0.03); BMI (SMD=0.28 KG/m^2, 95% CI (0.07, 0.50), p=0.01, (I^2=67%, p=0.40); T-cell count (SMD=0.09 G/L, 95% CI (-0.07, 0.26), p=0.26, (I^2=0%, p=0.73); Albumin level (SMD=0.28 G/DL, 95% CI (0.04, 0.52), p=0.02, (I^2=7%, p=0.34); IL-6 level (SMD=0.67, 95% CI (0.45, 0.90), p=0.00001, (I^2=94%, p=0.0001)) and LDH level (SMD=0.12 mmol/L, 95% CI (-0.05, 0.30), p=0.17.

Conclusion: This meta-analysis suggested that probiotics had significant positive effects on various measures for treating COVID-19.

Key words: Probiotics, Probiotic intervention, Probiotic treatment, Respiratory infections, COVID-19, SARS-CoV-2

Abbreviations: BMI: Body Mass Index; CD: Cluster of Differentiation; CI: Confidence Interval; COVID-19: Coronavirus Disease of 2019; CRP: C-Reactive Protein; FAO: Food and Agriculture Organization; IL-6: Interleukin-6; WHO: World Health Organization; LDH: Lactate Dehydrogenase; NCBI: National Center for Biotechnology Information; CFU: Colony Forming Unit; ORF: Open Reading Frames; RCTs: Randomized Controlled Trials; CNKI: China National Knowledge Infrastructure; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SD: Standard Deviation; SMD: Standardized Mean Difference.

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Introduction

In late December 2020, a novel and unfamiliar virus within the coronavirus family emerged in Wuhan, China, triggering a global health crisis [1]. This led to a state of emergency and overwhelming hospital facilities due to the rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The WHO officially declared this new disease a pandemic in March 2020 [1]. SARS-CoV-2 is an enveloped, single-stranded, positive RNA virus with a genome size of approximately 29.9 kb [2]. The genome consists of two main coding sequences orF1a and ORF1b, comprising 22 kb. These sequences are responsible for translating two polyproteins, which are subsequently cleaved into 16 nonstructural proteins crucial for viral replication [3]. The remaining 7.9 kb of the genome encodes four membrane glycoproteins, which form the virus's structure [2,3]. The virus spreads primarily through respiratory droplets, causing severe lung inflammation, cell destruction and ultimately death, particularly in adults [4]. Efforts to control the spread of the disease have led to the development of several vaccines, including the British "AstraZeneca", the Russian "Sputnik V", the Chinese "Sinovac", the European "Pfizer" and the American "Johnson & Johnson" [5]. While these vaccines have shown safety and efficacy to some extent, the continuous mutation of these viruses poses challenges. Variants such as delta and omicron necessitate ongoing research and the adoption of preventive measures [6]. There is a growing concern that current vaccines may become ineffective against future mutations, highlighting the need for alternative treatments [7]. Probiotics have emerged as potential therapeutic options due to their antiviral activity [8]. Defined by the FAO/WHO in 2001 as live microorganisms providing health benefits when administered in adequate quantities, probiotics offer a promising avenue for combating infections [9]. The use of probiotics, which originate from various sources, such as *Lactobacillus spp*., *Bifidobacterium spp*. and *Saccharomyces cerevisiae*, has a long history dating back to the early 1900s, when Elie Metchnikoff's research was conducted [10]. These microorganisms can be incorporated into various products, including yogurt and pharmaceuticals and have been studied extensively for their ability to prevent infectious diseases and modulate immune function [11]. Clinical studies, including randomized controlled trials, have demonstrated the efficacy of probiotics in mitigating COVID-19 symptoms and improving immune responses [16,17]. Probiotics have shown comparable or even superior outcomes compared to traditional treatments in some cases. This underscores their potential as a complementary approach to managing the disease. Additionally, concepts such as prebiotics, symbiotics, postbiotics and parabiotics have expanded our understanding of the therapeutic applications of probiotics, offering further avenues for research and development [16].

Methods

Study design

This meta-analysis, a quantitative analysis, utilizes statistical analyses to screen data sets, employing one or more representative schemes. The data were manually entered into the Cochrane Review, RevMan, version 5.4.1, to yield the analyzed data for scientific publication. The qualitative analysis was based on multiple scientific publications presented as studies of human randomized controlled trials.

Subjects and objective of the study

This meta-analysis aimed to investigate the effects of probiotics on the prophylaxis and treatment of coronavirus-related respiratory infections. Clinical research studies aim to reach conclusions, such as evaluating the effectiveness of probiotics for combating respiratory infections. The study aims to:

- Determine whether probiotics are more effective than other agents for prophylaxis.
- Assess whether efficacy varies based on dosage (treatment duration, age group) or species (*Lactobacillus spp*., *Bifidobacterium spp., etc.*).

The research questions are as follows:

- Do different probiotic species exhibit varying levels of effectiveness in preventing respiratory infections?
- Is there a disparity in the effect between drugs proven effective against COVID-19 and probiotics?

Research protocol

For the identification of relevant or similar studies, a search strategy was chosen utilizing the following databases: PubMed, NCBI (The National Center for Biotechnology Information), ScienceDirect, Springerlink, EMBASE, CNKI (China National of Knowledge Infrastructure) and Cochrane Library databases.

Search criteria

A search for relevant articles was conducted in the aforementioned databases between January 2020 and 2023. The search utilized keywords such as probiotic, probiotic treatment, probiotic intervention, probiotic prevention, COVID-19 disease, SARS-CoV-2, viral respiratory infection, randomized clinical trials and randomized controlled trials.

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Inclusion criteria

After reviewing the literature, titles and abstracts, the inclusion criteria were established as follows:

- Studies and articles available in English, French or Chinese, with full text accessible.
- Human randomized controlled trials with intervention and control groups or pre and postintervention study groups demonstrating clear outcomes.
- Studies examining the effects of probiotics on COVID-19 patients, regardless of demographic characteristics or health status.
- Use of probiotics from genera such as *Bifidobacterium, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Propionibacterium* and *Streptococcus*, whether alone or in combination with prebiotics, postbiotics or symbiotics.

Exclusion criteria

Following the literature review, titles and abstracts, the exclusion criteria were defined as follows:

- Studies lacking relevant outcomes or not meeting the RCT criteria.
- Studies in the form of conference abstracts, case reports, editorials, book chapters, reviews, commentaries, letters and similar articles with no relevant data.
- Trials with insufficient, unclear, incomplete or inaccessible data.
- Articles not investigating the measured variables.

Quality assessment

Quality assessment was independently conducted for each study based on the Cochrane risk of bias manual guidelines. Egger's tests were performed using Statistical Software for Data Science (STATA software), with a p value <0.05 indicating small study effects. The quality assessment considered seven elements: Random sequence generation, allocation concealment, blinding of participants and assessors, incomplete outcome data, selective reporting and other biases. Patients were categorized as low risk, high risk or unclear risk. Overall, study quality was rated as good, fair or poor [22].

Data extraction

The necessary data and information, including author(s), year of publication, study country, study design, participant characteristics (total number, age, sex), sample size of the intervention and control groups, probiotic source and type, dosage, duration of treatment and outcome precision, were extracted from each eligible RCT. Descriptive and statistical data for each outcome were collected.

Statistical analysis

The data from the included studies were analyzed using review manager 5.4.1 and STATA version 12.0. Mean (standard deviation) meta-analysis was performed and Standardized Mean Differences (SMDs) were calculated. Heterogeneity between study-specific estimates was assessed using the I^2 statistic and Cochran Q test, with I^2>50% or a p value <0.05 indicating significant heterogeneity. The Cochran Q test results are presented as I^2 values, defining heterogeneity as low (I^2<25%), moderate (25%<I^2<75%) or high (I^2>75%). The risk of bias assessment and risk of bias were evaluated using the Cochrane RevMan risk of bias tool. Publication bias was assessed visually through funnel plots and quantitatively using Egger's tests performed *via* STATA software, with a p value <0.05 indicating small study effects [21].

Results

Results of the selection studies

Table 1: Data extracted for inclusion in the meta-analysis.

Study (author, year)	Country	Study design	Participants	Intervention	Duration	Outcomes
Li Q, et al. 2021 [22]	China	Single-centercentre retrospective study	311 adult patients (≥ 18 years). 123 patients were treated with probiotics, 67 males and 56 females. The remaining 188 patients, 83 males and 105 females, received other	4 g of oral probiotics contain strains of: - 1.5 grams of Bifidobacterium, Lactobacillus, Enterococcus, Bacillus tablet and Bifidobacterium infantis. 2 grams of Bifidobacterium and Lactobacillus tablet (Bifidobacterium longum,	26 Days	08 selected laboratory parameters: (IL-6, CRP, LDH, total T cells, NK cells, B cells, CD4+ T cells, CD8+ T cells and CD4/CD8 ratio).

			drugs, for example, chloroquine phosphate.	Lactobacillus bulgaricus, Streptococcus thermophiles). - and finally, 0.5 grams of Bacillus subtilis and *Enterococcus Faecium* soluble capsules (*Enterococcus faecium*, *Bacillus subtilis*).		
Ceccarelli G, et al. 2021[23]	Italy	Observational and retrospective cohort study	The study involved 200 adult patients (≥ 18 years), consisting of 113 males and 87 females. - 112 patients received the BAT protocol without oral bacteriotherapy (probiotic). - 88 patients received the BAT protocol with oral bacteriotherapy.	Treatment by oral administration of SivoMixx formulations includes the probiotics: Lactobacillus brevis DSM 27961, Streptococcus thermophilus DSM 32245, Bifidobacterium lactis DSM 32246, Bifidobacterium lactis DSM 32247, Lactobacillus acidophilus DSM 32241, Lactobacillus helveticus DSM 32242, Lactobacillus paracasei DSM 32243, Lactobacillus plantarum DSM 32244, The formulation wasadministered in three equal doses per day, for a total of 24× 1011 CFU per day.	51 Days	(CRP, LDH, T cells, Albumin, Monocytes, BMI, PSI, Lymphocytes, White blood cells, Neutrophils, Duration of hospital stay (days), Deaths).
Gobbi M, et al. 2021[24]	Italy	Observational study	48 patients (26 males/22 females), 29 patients were treated with a nutritional intervention containing probiotics.	An oral intervention of fat-free milk powder contains vitamins, amino acids, minerals and probiotics: Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, A minimum of 1 to 1.3 g/day/kg of body weight. An optimal fat-to-carbohydrate energy ratio was 30:70, 50:50. Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei and Lactobacillus delbrueckii subsp. bulgaricus.	25 Days	This study included laboratory parameters measured from day 1 to day 7 of administration: (IL-6, CRP, T cells, albumin, ferritin, BMI, creatinine, serum iron), muscle strength (HG), performance test (TUG).
Araimo F, et al. 2021 [25]	Italy	An interventiona, non-pharmacological, open-label, randomized, prospective, double-blind study	85 patients (≥18 years) confirmed with COVID-19; only 28 patients were admitted to the study. - The first experimental group of 14 patients, known as the ozone group, was treated with the BAT protocol + O3-AHT therapy through the administration of	Intervention treatment of the administered SivoMixx product sachets contains probiotics: Streptococcus thermophilus DSM 32345, L. acidophilus DSM 32241, L.helveticus DSM 32242, L. paracasei DSM 32243, L. plantarum DSM 32244, L. brevis DSM 27961, B. lactis DSM 32246 and B. lactis DSM 32247. - Administration was only to the 14 patients, with	07 Days	This study included laboratory parameters measured from day 1 to day 7 of administration: (IL-6, CRP, T cells, albumin, ferritin, BMI, creatinine, serum iron), muscle strength (HG),

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			oxygen-ozone, followed by a duration of a probiotic mixture. - The second group of14 patients was treated with the therapeutic protocol only.	one sachet every 12 hours for 7 days. - Each sachet of SivoMixx in this study contained a high concentration of 8×109 CFU, administered every 12 hours.		performance test (TUG).
d'Ettorre G, et al. 2020[26]	Italy	A retrospective cohort study	70 COVID-19-positive patients - The first group of 48 patients received a BAT treatment protocol often containing hydroxychloroquine, antibiotics and tocilizumab. - The second group of 28 patients received oral bacteriotherapy (probiotic formulation).	The SivoMixx formulation administered in this study contained: Streptococcus thermophilus DSM 32345, L. acidophilus DSM 32241, L. helveticus DSM 32242, L. paracasei DSM 32243, L. plantarum DSM 32244, L. brevis DSM 27961, B. lactis DSM 32246 and B. lactis DSM 32247. - This oral bacteriotherapy involved the use of 24×1011 CFU per day. - The formulation was administered in three equal doses per day.	17 Days	This study includes respiratory parameters: (FiO2, SO2, pH, HCO3-, pO2, pCO2) and BMI.

Results of the risk bias assessment

The assessment of quality and risk of bias in the included studies was based on seven key areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases [22-26]. This assessment relies on established criteria outlined in the "Cochrane Handbook for Systematic Reviews of Interventions" to evaluate the likelihood of bias in each domain. The nature of risk was categorized as "high risk," "low risk," or "unclear risk" for each study, considering its methodological quality and potential biases **(Figures 1, 2 and 3)**.

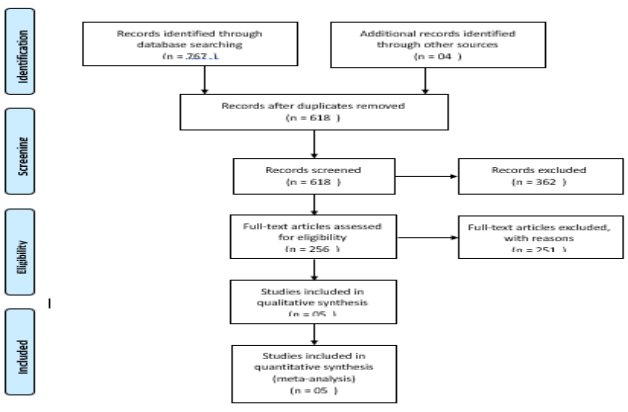

Figure 1: PRISMA Flowchart for the study selection process.

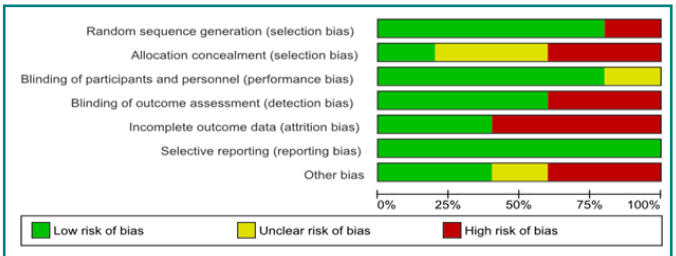

Figure 2: Graph Showing the risk of bias of the included studies.

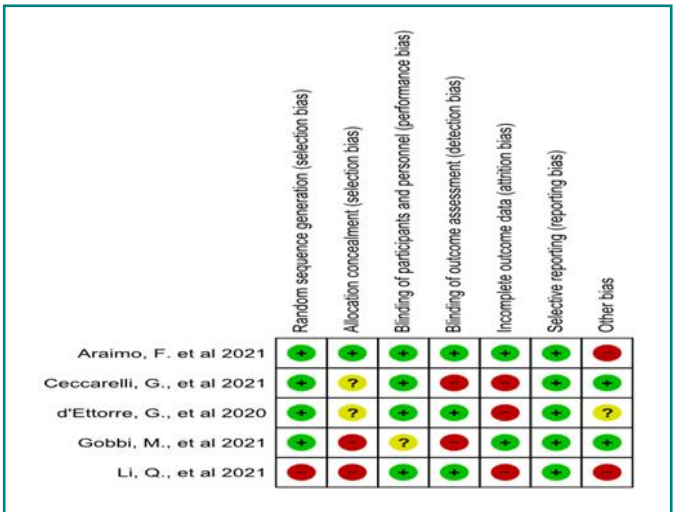

Figure 3: Graphical representation of the risk of bias in percentage (%).

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The rationale for the application of probiotics as a potential prevention and alternative treatment strategy against COVID-19

A meta-analysis was also conducted to analyze existing studies in the literature. Our focus was on probiotic treatment for respiratory infections. Q-statistics were employed to evaluate whether effect sizes across individual studies were homogeneous, indicating the degree of heterogeneity. Additionally, heterogeneity of individual outcome estimates in the meta-analysis was assessed using forest plots. The efficacy of probiotics varies based on the specific strains, age groups, clinical dosages and mode of administration. Clinical studies, including randomized, double-blind, intervention-controlled or experimental human trials of probiotics, were planned. The overall effects of probiotics were quantified using values such as Standardized Mean Differences (SMDs) and Confidence Intervals (CIs) [27].

Selection of parameters or outcomes in the analysis

The five included studies were human clinical trials involving COVID-19 patients experiencing respiratory difficulties due to inflammation. A total of 657 patients were divided into two groups, each of which were treated with specific therapeutic protocols that included probiotics from various strains (such as Bifidobacterium, Lactobacillus and Streptococcus) sourced from products such as SivoMixx, capsules and milk powder. Following the treatment period in each trial, posttreatment monitoring of patients' immune and health status was conducted. This assessment involved various parameters, including blood test results and respiratory status evaluation results and was administered by specialists across all the studies. Among these parameters, CRP, BMI, T cells, albumin, IL-6, LDH and ferritin were identified as common outcomes across all five studies for subsequent analysis **(Figure 3)**.

Probiotics and C-Reactive Protein (CRP)

The CRP level serves as an indicator of inflammation and is commonly associated with respiratory infections caused by COVID-19 [28]. It is a protein involved in the acute phase of inflammation and its levels increase in the serum or plasma during response to infections or early inflammatory events [29]. With regard to this parameter, a meta-analysis of four studies based on five RCTs involving 587 participants (254 in the experimental group and 333 in the control group) revealed an overall significant effect (p=0.002), with a Standardized Mean Difference (SMD) of 0.26 and a Confidence Interval (CI) of 0.10 to 0.43 [22-25]. The analysis showed a statistically significant increase in CRP levels (p=0.002<0.05), indicating significant heterogeneity **(Figure 4)**.

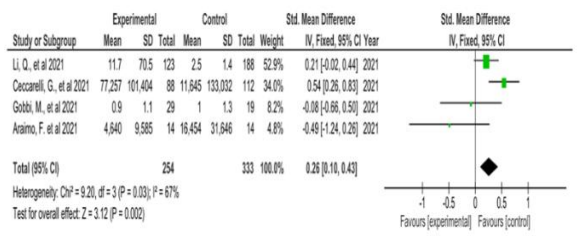

Figure 4: Forest plot showing the association between experimental probiotic use and other control interventions on CRP levels.

Probiotics and Body Mass Index (BMI)

Body Mass Index (BMI) is a widely used measure for assessing individuals' corpulence and tracking changes in body composition over time. Body Mass Index (BMI) was calculated based on height and body mass and served as an indicator of overweight and obesity according to WHO guidelines, with the formula BMI=P/T2 or BMI=m×h-2 [30].

In the analysis of BMI across four studies from five RCTs involving 346 patients (159 in the test group and 187 in the control group), there was an overall increase in BMI (SMD 0.28; CI 0.07-0.50; p=0.01) [23-26]. This finding indicated a significant increase (p=0.01<0.05) in BMI. Notably, the included studies exhibited low heterogeneity, which was not statistically significant (I2=0%; p=0.40>0.05) **(Figure 5)**.

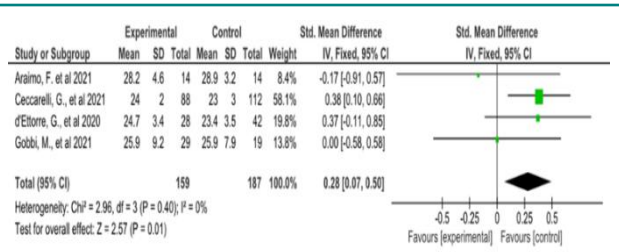

Figure 5: Forest plot showing the association between experimental probiotic use and other control interventions on BMI.

Probiotics and T cells

The T-cell count serves as an indicator of the adaptive immune response, offering insight into the cellular immune status, particularly in coronavirus-affected lung cells [31]. T cells, including subsets such as CD4+ T cells, CD8+ T cells, B cells and Natural Killer (NK) cells, are crucial for maintaining immune system function post viral infection [32].

In the context of T-cell analysis across four studies from five RCTs, involving 587 participants (254 in the experimental group and 333 in the control group) included

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in this meta-analysis, each individual was treated with probiotics [22-25]. The overall effect revealed a nonsignificant increase (p=0.26>0.05), with a Standardized Mean Difference (SMD) of 0.09 and a Confidence Interval (CI) of -0.07 to 0.26 (p=0.26). Notably, the included studies exhibited a complete lack of heterogeneity, indicating a low and statistically nonsignificant level (I2=0%; p=0.73) **(Figure 6)**.

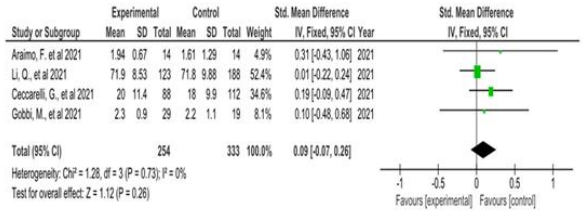

Figure 6: Forest plot showing the association between experimental probiotic use and other control interventions on T-cell counts.

Probiotics and albumin

Albumin levels serve as indicators of enzyme, drug and hormone transport, as well as blood circulation stabilization [33]. As an acute-phase reactant with antioxidant properties, plasma ALB is crucial for scavenging Reactive Oxygen Species (ROS) under normal physiological conditions [34]. In cases of oxidation, ROS accumulation in neutrophils triggers extracellular neutrophil traps, which can accumulate in the lungs, as observed in COVID-19 cases [34].

Analysis of three studies from five RCTs involving a total of 276 participants (131 in the experimental group and 145 in the control group) revealed an increase in the serum ALB concentration following probiotic supplementation [23-25]. The overall effect of this increase was significant (p=0.02), with a Standardized Mean Difference (SMD) of 0.28 and a Confidence Interval (CI) of 0.04 to 0.52, as indicated by the p value (p=0.02<0.34) **(Figure 7)**.

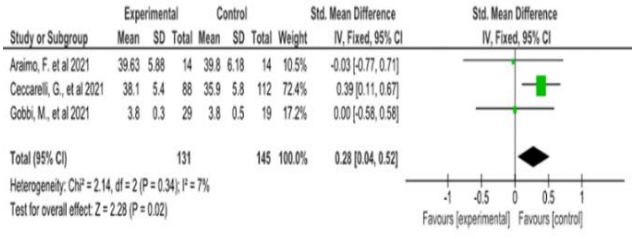

Figure 7: Forest plot showing the association between the use of experimental probiotics and other control interventions on the serum Albumin concentration.

Probiotics and IL-6

Only two out of the five RCTs, involving 339 patients (137 in the first group and 202 in the second group), demonstrated a significant increase in interleukin-6 levels following the administration of probiotic formulas [22,25]. Interleukin-6 is produced by the immune system as part of the defensive response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which involves the intervention of various white blood cells, including macrophages, T cells and B cells [35].

The meta-analysis revealed a significant increase in the pooled effect (p=0.00001) (SMD=0.67; CI=0.45-0.90) (p=0.00001<0.05). Furthermore, a high level of heterogeneity (I2=94%) was observed, which was considered significant given that the p value (p=0.0001) was less than 0.05 **(Figure 8)**.

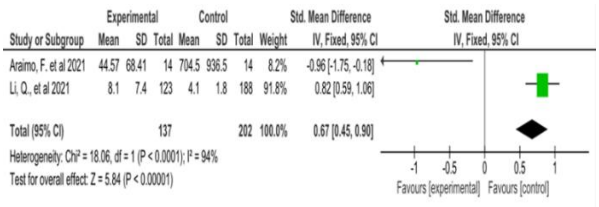

Figure 8: Forest plot showing the association between. experimental probiotic use and other control interventions on IL-6 levels.

Probiotics and LDH

LDH levels serve as a nonspecific indicator of cell death in patients with various respiratory diseases, including COVID-19 [36]. Lactate Dehydrogenase (LDH) is an enzyme crucial for the conversion of lactate to pyruvate in most body tissues and its levels typically increase following tissue breakdown, reflecting elevated serum LDH in numerous clinical conditions [37].

In this context, only two out of five RCTs [22, 23] involving 511 confirmed COVID-19 patients (211 in one group and 300 in another) included in the meta-analysis demonstrated a decrease in LDH levels among patients receiving probiotics. However, the overall association between probiotic intervention and LDH levels was nonsignificant, with a p value of 0.17 indicating no statistical significance (SMD 0.12; CI -0.05 to 0.30; p=0.17). Additionally, the included studies exhibited moderate heterogeneity (I2=55%; p=0.13), which was not statistically significant (p=0.13<0.05) **(Figure 9)**.

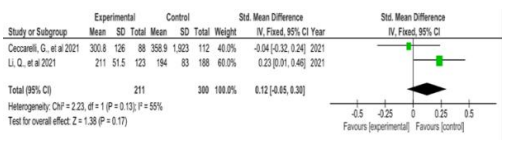

Figure 9: Forest plot showing the association between experimental probiotic use and other control interventions on LDH levels.

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Probiotics and ferritin

Ferritin serves as a vital protein for iron storage, facilitating iron availability for crucial cellular processes while safeguarding DNA, lipids and proteins from the potential toxic effects of iron. Blood sampling of ferritin is essential, given its involvement in various diseases, including inflammatory, neurodegenerative and malignant conditions [38].

In this analysis, only two out of five RCTs involving a total of 76 participants contributed to the meta-analysis, revealing an increase in ferritin levels following probiotic intake [24,25]. However, the overall association between probiotic usage and ferritin levels was not significant, with a p value of 0.41 (Standardized Mean Difference (SMD) 0.19; CI -0.27 to 0.66; p=0.41<0.05). Notably, the included studies exhibited a significantly greater level of heterogeneity (I^2=77%; p=0.04) **(Figure 10)**.

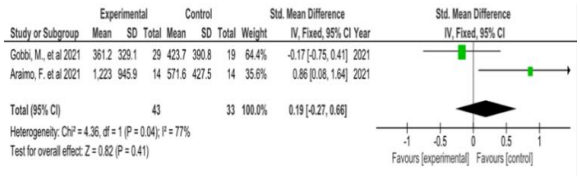

Figure 10: Forest plot showing the association between experimental probiotic use and other control interventions on ferritin levels.

Results of the Publication Bias Assessment

The funnel plot, depicted in **figure 11**, illustrates minimal indications of publication bias across the five selected studies. The funnel plots graphically represent the curves constructed for the analyzed parameters: CRP concentration, BMI, T-cell count, albumin concentration, IL-6 concentration, LDH concentration and ferritin concentration, facilitating the assessment of bias in each included study. Of particular interest are the p values obtained from the Egger test, which were 0.0001, 0.04, 0.13, 0.34, 0.40, 0.40 and 0.73 for the respective parameters. Notably, most of these values were statistically insignificant, as they exceeded the threshold of 0.05, except for IL-6 (p=0.0001), indicating a small study effect. Consequently, only one parameter, IL-6, exhibited bias, while the remaining six parameters showed no signs of publication bias.

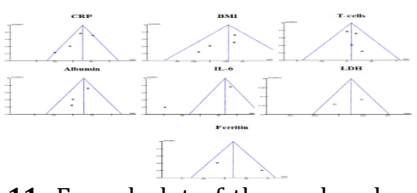

Figure 11: Funnel plot of the analyzed parameters (CRP level, BMI, T-cell count, albumin, IL-6, LDH and ferritin).

Discussion

Discussion of the quality of the included studies

Random sequence generation

The random sequence generation index pertains to the randomization process of participants into intervention groups [39]. Among the five included studies, four demonstrated a low-risk percentage of 80%, while the remaining study was assessed as high risk, constituting 20% of the total [23-26]. This discrepancy can be rationalized by contextual factors. The study categorized as high risk was conducted relatively early in the context of the SARS-CoV-2 outbreak compared to the others [22]. Initiated in February 2020, when knowledge about COVID-19 was limited, researchers might have faced challenges in ensuring fully randomized participant allocation. The constraints imposed by the emergent nature of the crisis could have restricted opportunities for randomization and necessitated organizational adjustments in the study design. Despite these limitations, the study is pertinent because it investigates the impact of probiotics, specifically in capsule form, aligning with the overarching objective of the meta-analysis.

Allocation concealment

The second criterion, allocation concealment, pertains to the detailed description of methodological procedures aimed at concealing the interventional allocation sequence [39].

Among the five studies, two were deemed to have a high risk, accounting for 40% of the total [22,24]. In the case of study, the inability to prognosticate the health status of patients and the high possibility of complications during the emergent phase of the COVID-19 outbreak rendered concealment impractical [22]. The study [24] was also categorized as high risk because participants were admitted to rehabilitation services after exiting the acute phase of COVID-19, necessitating increased monitoring and targeted nutritional interventions.

Additionally, two studies, representing 40% of the total, were characterized by unclear bias due to a lack of information available for assessing the risk level [23,26]. Conversely, the remaining study, constituting 20% of the total, was assessed as low risk [25]. This classification was based on the minimal scale of participants (only 28), enabling independent and closely monitored therapeutic procedures.

Blinding of participants and personnel

This third criterion describes all the measures used, if any, to blind study participants to the nature of the interventions they received and staff to know which group they were assigned to [39].

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4 of the 5 studies evaluated as low risk covered a percentage of 80% because the patients in these studies did not know which intervention group they belonged to [22-26]. Blinding of participants in human clinical studies is often recommended because it has a clear positive influence on the body's response and psychological state, which provides results and sometimes ensures perfect resistance against diseases. This leads the patient to believe that they are receiving effective treatment and the same applies to the remaining patients to avoid bias in the results. Thus, for a correct study of the real effect of each treatment against the other, blinding is essential.

The remaining study of 5, was scored as indefinite risk because it was unclear and lacked sufficient information for this procedure [24].

Blinding of outcome assessment

The fourth criterion of this assessment refers to the process of concealing the identity of the treatment group from the outcome assessors after their assignment to the treatment by randomization to minimize the occurrence of biased assessments influencing the outcome of the research [39].

3 Studies out of 5 were rated as low risk, covering a percentage of 60% [22,25,26]. In that study, the epidemiological and clinical characteristics of each patient and laboratory parameters were monitored and collected occasionally by people independent of the specialists, which facilitated the use of probiotics or hydroxychloroquine [22]. The study did not reveal serious health changes that required the intervention of previous clinicians to administer the treatment to the 28 participants [25]. In one study, during admission, the participants underwent blood tests and after continuous dosing of oxygen with probiotics and drugs was administered to each group, the clinicians did not repeat the gas and blood analysis, considering that periodic monitoring was unnecessary [26].

The remaining 2 studies were considered to be at indefinite risk and covered a percentage of 40% [23,24]. In [23], a set of measures was implemented to predict several changes (blood urea, blood pressure and respiratory rate) to achieve the goal of reducing mortality as much as possible. One study considered it necessary to carry out blood tests periodically to assess the effectiveness of the mentioned interventions on muscle strength and the restoration of physical conditions [24].

Incomplete outcome data

The fifth criterion provides a comprehensive description of the outcome data for each primary outcome, including attrition and exclusions from the analysis (death, withdrawal) or due to the complication of certain health conditions in each intervention group [39].

3 out of 5 studies were assessed as high risk, comprising 60%, due to the exclusion of patients out of the total number, usually due to deaths in all three studies [22,23,26]. One study reported a total of 44 deaths in females and males [23]. In [26], participants died, but the exact number of deaths was not specified; complications resulting from elevated serum IL-6 levels indicate deteriorating health. In [22], there were many exclusions due to death; 30 people died in the probiotic group, which is far fewer than in the other group.

The remaining 2 studies out of 5 were considered low risk, covering 40%, meaning that no participants were excluded for these reasons [24,25]. In [25], 28 participants completed the study successfully without any deaths. In [24], 48 participants completed the study without withdrawal or death.

Selective reporting

The sixth criterion revealed how the possibility of selective outcome reporting was examined by the review authors and what was found raises the following question: Are the study reports free from suggestions of selective outcome reporting? [39].

All 5 studies are rated as low risk, comprising a percentage of 100%, as all protocols used in the studies are available and advised by associations and organizations and all specified outcomes (primary and secondary) have a prespecified impact [22-26].

Other biases

The final criterion of other biases describes the status of significant concerns about bias not addressed in the previous six areas, generally by limitations of each included study [39].

2 Studies out of the 5 showed a low risk of bias, comprising a percentage of 40%, as they lacked serious biases and major limitations that may hinder or limit the course taken by these studies [23,24].

Then, 2 out of 5 were noted as high risk, covering a percentage of 40% [22,25]. Several limitations of the present study are reported, including the small sample size, the short follow-up period and the inability to determine the specific effects and exact influence of the different drugs used [25]. An important limitation of the present study is that the retrospective study was monocentric in design and involved the use of a single source [22]. In the future, large-scale studies are needed to obtain high-quality evidence and thus exclude patients who died from COVID-19.

Finally, the remaining study was assessed as being of unclear risk, as there are no reports of bias regarding the limitations of this study [26].

Discussion of the parameters analyzed

In the discussion and interpretation, the parameters analyzed necessarily depend on the location on the vertical

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axis, either on the left or on the right, depending on the intervention effect of each included study.

- The effect is displayed on the left (considered in favor of the control) when the value is SMD<0.00.
- The effect was located in the right-hand position (considered in favor of the intervention groups, generally experimental) when the value was SMD>0.00.
- The average position in the middle indicates no effect when the value is SMD=0.00.

C-Reactive Protein (CRP)

The first parameter, CRP, which indicates the degree of inflammation, was analyzed in 587 patients. We noted **(Figure 4)** that there were 4 studies out of 5 after the intervention of probiotics from different sources (drugs, nutritional food supplements) that belong to different strains (*Lactobacillus, Bifidobacterium* and *Streptococcus*) [22-25].

According to 2 of 4, the probiotic agents had SMDs in the following order: -0.08 MG/L, including an increase in CI (-0.66 to 0.50) and -0.49 MG/L, also with an increase of (-1.24 to 0.26) [24,25]. These two devices were placed on the left of the vertical axis, meaning that this position can be translated to a favorable effect in the control group according to these two studies.

The remaining studies showed other SMDs in the range of 0.21 MG/L with an increase [CI: -0.02-0.44] and 0.54 MG/L [CI: 0.26-0.83] placed in the right position of the vertical axis, which means that there is an effect in favor of the intervention and an increase compared to the previous values; this difference translates into COVID-19 replication in lung cells [22,23].

The black diamond at the bottom of the table summarizes the overall effect of all previous interventions in each study included in the analysis of this endpoint. Its positioning corresponds to the statistical calculations of the mean between the confidence interval and the SMD. This effect translates into an overall value of the SMD center, which is 0.26 MG/L, a statistically insignificant increase in adverse effects after a set of probiotic administration and intervention procedures. It is important to note that study, with the highest SMD effect of 0.54 MG/L (high inflammation), showed that clinicians used the therapeutic protocol in both groups (experimental and control). Only those with respiratory complications due to inflammation received high doses of probiotics [23]. This explains the negative influence of probiotics on the inflammation index (CRP) in the experimental group. However, overall, we found that the survival of patients was greater than that of patients treated with probiotics.

The cause of the high CRP levels in the experimental groups was inflammation caused by COVID-19, which mainly affects the lungs and was much greater in the experimental group than in the control group. In contrast, several scientific publications based on human or animal trials have shown the positive effect of probiotics and suggested that they are a better alternative to other drugs used in the Control Group to Reduce inflammation levels (CRPs) caused by respiratory viruses, which have a similar mechanism of action to that of COVID-19, such as influenza H7N9. The results showed a nonsignificant effect for the probiotic groups [40,41].

However, these findings are insufficient and in the future, additional randomized studies are needed to better understand the impact of probiotics on the inflammation indices of patients with COVID-19. Better results can be obtained with the proliferation of studies on the subject. The insufficiency of journals that address these pathologies and the research, still at the experimental level, does not allow for an exhaustive and definite opinion on the issue.

Body Mass Index (BMI)

The second parameter, Body Mass Index (BMI), which is a quick indicator of copulence with weight and height, was included in the quantitative analysis **(Figure 5)**. This included 4 out of 5 studies, covering a total of 346 participants [23- 26]. Only one out of four studies was on the left side of the vertical axis after treatment with probiotics and administration of an oxygen/ozone (O2/O3) mixture. This resulted in an SMD of -0.17 KG/m^2 with subsequent increases [CI: -0.91-0.57], indicating an effect in favor of the control group.

We observed that one study used the mean middle of the vertical axis with an SMD value of 0.00 KG/m^2 after the use of probiotics contained in milk powder [24]. This means that there was no change in this index before or after therapeutic nutritional treatment in either group.

Then, two studies took the right position of the vertical axis after the intervention of probiotic strains from the same source (SivoMixx) but at different high concentration doses (16×10^9 and 24×10^{11} CFU/per day) [23,26]. These showed SMD values of 0.37 KG/m^2 and 0.38 KG/m^2, indicating an effect in favor of the probiotic intervention experimental groups.

Finally, the marker consisting of the black diamond on the graph had a value of SMD=0.28 KG/m^2, a significant increase indicating a beneficial effect in the experimental group, which generally received probiotics. To prove the viability of our results, a recent study showed the beneficial impact of probiotic strains (*Lactobacillus*, *Bifidobacterium* and *Streptococcus*), the same ones used in our clinical experiments, on reducing URTI symptoms [42]. This study revealed the impact of COVID-19 infection on

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body mass index in adults and children, which resulted in weight loss and improved metabolic parameters, which positively affected BMI.

T cells

The third parameter analyzed, T cells, are the basis of adaptive immunity, as they manufacture and aggregate several immune cells (CD4, CD8 and NK cells) and help motivate B cells to manufacture antibodies against microbial agents [32].

For the evaluation of total T cells, 4 studies out of 5 included this parameter in the meta-analysis **(Figure 6)** [22-25]. The four studies had variable SMD values in the following order: 0.01, 0.10, 0.19 and 0.13 after treatment with the original probiotics (supplements, nutritional material sub form or capsules), indicating a significant effect in favor of the experimental group.

Among the four included studies, there was diversity in the effect and extent of the immune response in each study, as shown by comparison of SMD values. Although 2 out of 4 the probiotics that were orally administered were from the same source (SivoMixx), they had values of 0.19 G/L according to previous studies and 0.31 G/L [23,25]. This leads to the important observation that this difference is a direct result of the doses administered (24×10^{11} CFU/per day $>16 \times 10^{8}$ CFU/per day), which results in these clearly distinct effects; *i.e.,* when the amount of probiotics increases, a more positive effect on the T-cell count can be observed; however, the doses must, of course, respect the limits imposed by the FAO and WHO in 2002 [43].

The overall effect size of the included SMD studies was estimated to be 0.09 G/L and the increase was within the confidence interval of [-0.07-0.26], which translates to a significant increase in a small effect but is still the best possible index.

In fact, according to the World Health Organization (WHO), when COVID-19 replicates in cells, it often has subterfuge effects, preventing the resistance of immune cells, generally T lymphocytes. When HELSTs penetrate cells, they only express long external coronary receptors, which are involved in the total protein composition. In this sense, cells can grow as a protein support (energy), which helps them relax their defense, thus preventing the involvement of T cells. Instead, the viral load continues to increase until the body collapses. The results revealed the role of probiotics in increasing T-cell levels, which are involved in resistance against all undesirable agents (as shown in our results indicating an immune response against COVID-19). Several reviews highlight one of the main characteristics of probiotics in modulating the immune system [44].

Albumin

For the determination of albumin levels, 3 out of 5 studies were included in the analysis **(Figure 7)**, involving the intervention of probiotics and other therapeutic protocols such as hydroxychloroquine, tocilizumab and O2/O3 administration, with the SMD values of each study amounting in order: -0.03, 0.00, 0.39 [23-25].

A study with a value of -0.03 indicates an effect in favor of the control group. A value of 0.00 indicated no change in the serum ALB concentration in the two treatment groups and a final SMD of 0.39 indicated an effect in favor of the experimental group that generally received probiotics.

The black diamond, summarizing the overall effect size in these experiments, shows an SMD value of 0.28 G/DL, indicating a significant increase in the serum ALB concentration. Moreover, the positive effect of this blood index in favor of the participants in the experimental groups who received probiotics is supported by the study [45]. The increase in the serum ALB concentration in those consuming probiotics compared to that in the control group was 0.2 G/dL, up to 3.4 G/dL. This increase in albumin levels translates to good transport of enzymes, hormones and many substances that provide the necessary elements for the body as they circulate in the blood [46].

IL-6

To determine the fifth parameter, interleukin 6 (IL-6) and 2 SMD values were calculated after the analysis of 2 out of 5 studies **(Figure 8)** [22,25]. The SMDs are as follows: a large effect in favor of the control group, 0.06; with a confidence interval between (-1.75 to -0.18) and another small effect compared to the experimental group.

The overall effect of the two SMDs was 0.67, reflecting a significant increase in IL-6 levels. This indicates a statistically significant calculation in favor of the experimental groups that received probiotics, in contrast to the control groups of these 2 studies included in this parameter, which did not receive this oral bacteriotherapy. This increase in IL-6 suggested good anti-inflammatory activity against COVID-19 in the probiotic experimental group.

LDH

Regarding lactate dehydrogenase, a total of 2 studies out of 5 were analyzed **(Figure 9)**, revealing different positions on the left and right vertical axes after treatment with probiotics (*Lactobacillus, Bifidobacterium, Streptococcus*), hydroxychloroquine, lopinavir/ritonavir, tocilizumab*, etc.* [22,23]. Analysis of the statistical data of these two studies after blood sampling at the end of the treatment duration yielded the following SMDs: -0.04 mmol/L (favoring the control group) and 0.23 mmol/L (favoring the experimental group).

The overall effect of this parameter analysis showed that the consumption of probiotics increased the LDH level to 0.12 mmol/L, representing almost a minimal effect in

favor of the experimental group. This increase was statistically nonsignificant. The study by demonstrated a nonsignificant effect of probiotics, with results differing (showing a decrease in LDH levels treated by probiotics) from our study due to the reduced number of articles included in the meta-analysis of this index [47].

Ferritin

Finally, for ferritin, after the previously mentioned two-group treatment procedures, only 2 studies were included in the analysis out of 5 **(Figure 10)** [24,25]. This illustrates that there are 2 vertical axes, each taking different positions, including SMD values rising from -0.17 mmol/L, according to the study by [24], in favor of the control group and 0.86 mmol/L in favor of the test group, for patients with COVID-19 [25].

The overall effect size of the studies included in the analysis showed a significant increase in favor of the probiotic-treated groups, with an SMD of 0.19 mmol/L. This finding indicates an increase in ferritin levels in favor of those consuming probiotics. For example, in the present study, more (24 × 1011 CFU) cockroaches were consumed.

The increase in ferritin levels explains the good availability of iron in the bloodstream to compete against respiratory tract infections, which are the main symptoms of COVID-19.

Conclusion

In conclusion, probiotics, which have been demonstrated to be effective at modulating the immune system and gut microbiota, are essential agents for the prophylaxis and treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The present meta-analysis involved the selection and filtration of 776 articles from seven databases. In addition to the data extraction and statistical analysis of 5 studies structured according to 7 parameters, we were able to assess the incidence of respiratory infections related to COVID-19, which is a main symptom.

Quantitative analysis of the data from the 5 included studies indicated a statistically nonsignificant increase in LDH levels and inflammatory indices, including CRP levels, with a lack of significance according to the degree of heterogeneity (I^2=0%) and a statistically significant increase in each of the following parameters: BMI, T cells, albumin, IL-6 and ferritin, with varying levels of heterogeneity ranging from low to high.

This meta-analysis, based on human randomized clinical trials, highlights the need for additional clinical data in the near future to fully identify the specific role of probiotics in SARS-CoV-2-related respiratory infections. Further investigations of RCTs need to be conducted through additional research. During our search for eligible studies to be included in this analysis, we encountered significant difficulties in gathering sufficient information to provide a comprehensive overview of the issue. This problem can be addressed by conducting more specific and confidential experiments involving the blinding of participants, investigators and researchers, as well as larger sample sizes and multicenter studies. Such efforts will contribute to improving our understanding of the efficacy of probiotics in combating COVID-19-related respiratory infections.

Competing interests

All authors declare that they have no competing interests. All authors have no conflicts of interest to disclose.

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