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Revisão

# *Lactobacilli* species' effects on liver function: a review

## *Efeito de espécies de Lactobacilos na função hepática: uma revisão*

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## ABSTRACT

Probiotics are microorganisms that, when ingested, colonize the gastrointestinal tract and bring health benefits. An unbalanced microbiota is synonymous with several diseases, promoting bacterial translocation to other body organs, especially the liver. Given the close correlation between these two factors and the recognized safety of daily intake of probiotics, this literature review aims to collect data on the impact of *Lactobacilli* probiotics on human liver function. The search for clinical studies published between the years 2011 and 2021 was carried out in the following databases and search tools: SciELO (Scientific Electronic Library Online), Google Scholar, PubMed, BVS (Virtual Health Library), Embase, Science Direct, Scopus, CRD (Centre for Reviews and Dissemination) and the Cochrane Library. The articles obtained at the end of the research brought data support the idea that the supplementation of probiotics containing bacteria of the genus *Lactobacilli* is beneficial for patients with a wide range of liver disorders, such as cirrhosis and hepatic encephalopathy. The mechanisms behind this action are diverse, such as decreased intestinal permeability, the growth of pathogenic microorganisms, and pro-inflammatory factors, in addition to stimulating colonization by symbiotic bacteria. Furthermore, studies carried out with healthy patients demonstrate the safety of probiotics, with no adverse effects.

**Keywords:** *Lactobacillus*; probiotic; liver function.

## RESUMO

São chamados de probióticos os microrganismos que, quando ingeridos, colonizam o trato gastrointestinal e trazem benefícios a saúde. Uma microbiota desbalanceada é considerada sinônimo de diversas doenças, ao promover translocação bacteriana para os demais órgãos do corpo, em especial, o fígado. Dada a estreita correlação entre esses dois fatores, bem como a reconhecida segurança da ingestão de probióticos no dia a dia, a presente revisão bibliográfica tem como objetivo o levantamento de dados sobre o impacto dos probióticos Lactobacilos na função hepática humana. A busca por estudos clínicos publicados entre os anos de 2011 e 2021 foi realizada nas seguintes bases de dados: SciELO (*Scientific Electronic Library Onlin*e), Google Acadêmico, PubMed, BVS (Biblioteca

Virtual em Saúde), *Embase, Science Direct, Scopus,* CRD (*Centre for Reviews and Dissemination*) e *Cochrane Library*. Os artigos obtidos ao final da pesquisa trouxeram dados que apoiam a ideia de que a suplementação de probióticos contendo bactérias do gênero Lactobacilos é benéfica para pacientes com as mais variadas desordens hepáticas, tais como cirrose e encefalopatia hepática. Os mecanismos por trás dessa ação são diversos, tais como: diminuição da permeabilidade intestinal, bem como do crescimento de microrganismos patogênicos, e fatores pró-inflamatórios, além do estímulo de colonização por bactérias simbiontes. Ainda, estudos realizados com pacientes saudáveis demonstram a segurança do uso de probióticos, com ausência de efeitos adversos.

**Palavras-chave:** *Lactobacillus*; probióticos; função hepática.

## INTRODUCTION

Liver-related diseases are major health problems that affect a large portion of the population. According to a study conducted in the United States of America (USA) in 2002, about 72 people out of 100.000 had some chronic liver disease. For example, one can cite the 20% prevalence of alcoholic hepatitis in people aged 40 to 60 (1). In 2019, an even more worrying fact emerged: liver cirrhosis is the eleventh leading cause of death worldwide (2). Also, according to data published by the Global Burden of Diseases, Injuries and Risk Factors Study 2017, globally, 1,5 billion people live with chronic hepatitis and liver cirrhosis (3), and another 311 million are infected with hepatitis B and C viruses (4).

Several liver disorders are characterized by the presence of fat in the liver, as well as inflammation, necrosis, and an increase in aminotransferases (5), which lead to loss of quality of life, secondary injuries, and death. These diseases have become as problematic as obesity worldwide (6). It is worth remembering that many hepatic pathologies do not have an established pharmacological therapeutic protocol, with the basic treatment changing in lifestyle (5, 7).

In this context, there is a close relationship between the intestine and the liver since the liver receives blood directly from this portion of the gastrointestinal tract through the portal circulation. The microbiota in this large organ of the digestive system is thought to impact liver function (5) through the interaction between about 2000 species of bacteria. The gut microbiota maintains the homeostasis of various body systems, such as the immune system and digestion. Changes in the composition and balance of the microorganisms involved can lead to or worsen disease conditions such as diabetes, obesity, and irritable bowel syndrome (1). With this in mind, the scientific community turns its eyes to maintaining intestinal microbiota balance through the consumption of probiotics.

Probiotics are microorganisms that benefit the organism when consumed in adequate amounts. Its ability to inhibit the growth of pathogenic bacteria by competing for nutrients and its adherence to the intestinal epithelium can be mentioned, promoting an improvement in bacterial translocation to other tissues (7,8), which culminates in a lower production of inflammatory molecules (5). Among them, the most famous are lactic acid bacteria, especially *Lactobacilli* (9), known for their beneficial role in other pathologies, such as constipation, diarrhea, lactose intolerance, cancer, obesity, and disorders of the lipid profile. In addition, they are considered safe for human consumption and widely used in preparing yogurts, cheeses, and other fermented foods (9-11).

To contribute to the studies related to the Gram-positive bacteria of the genus *Lactobacilli* and seek materials in the context of improving liver function, the present study aimed to investigate the impact of the consumption of probiotics containing *Lactobacilli* on the liver and liver diseases.

## METHODS

The databases selected for the research of the materials that make up the collection of this bibliographic review were: SciELO (Scientific Electronic Library Online), Google Scholar, PubMed, BVS (Virtual Health Library), Embase, Science Direct, Scopus, CRD (Center for Reviews and Dissemination) and the Cochrane Library, to have broad coverage on the topic.

### INCLUSION CRITERIA

Articles published between 2011 and 2021, written in Portuguese, English and Spanish, focusing on evaluating the impact of *Lactobacilli* species on human liver function through clinical trials, were included.

**Exclusion criteria.** Exclusion criteria are listed below: (i) books, opinion articles, review articles, and conference banners; (ii) those with a language or date restriction; (iii) studies that did not assess liver function or did not use *Lactobacilli*; (iv) cell culture experiments, *in vitro* or with the use of animals; (v) studies that used probiotic associations with other molecules or prebiotics; (vi) unfinished studies or studies not available for full access.

**Sources of information and strategies for search.** The search strategy used in each database was adapted to the search needs of each of them. The terms chosen were "*Lactobacillus*" and "Hepatic function", as well as their Portuguese counterparts, which were confirmed through a DeCS/MeSH survey (Table 1).

**Studies selection.** The first step of this literature review was the search for materials using the terms adapted to each database. Subsequently, the found references were added to EndNote Web, an online citation management program, to exclude duplicates. The title and abstract were read during the third stage, culminating in removing works that did not respect the previously established criteria. Finally, in the fourth step, the last exclusion was made through the entire reading of the remaining materials. Relevant information from the materials that make up the definitive collection of this review was extracted, including year and language of publication, country of study, clinical trials methodology (randomization, blinding, number of participants in each group and their characteristics, species of probiotic bacteria, dosage regimen, duration of interventions), and final outcomes analyzed.

**Risk of bias.** The assessment of the risk of bias in the clinical trials of this review was performed using the Cochrane Risk of Bias Tool, which evaluated parameters for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. For each, a high, low, or uncertain risk rating was assigned (12,13).

## RESULTS AND DISCUSSION

With the initial search in databases, 3643 materials were found. After inserting them in the EndNote Web reference manager, 491 duplicate articles were observed. Of the 3152 remaining materials, 3009 were eliminated after analyzing the title and abstracts since it was perceived that they did not fit the pre-established criteria. The 143 remaining articles were entirely read, excluding 115 more materials. The collection of the present review was based on the data obtained from 28 clinical studies (Figure 1).

### CHARACTERIZATION OF MATERIALS

The materials included the years 2011 to 2021, written in English. Only 20 articles confirmed in their methodology that they were double-blind studies. At the same time, one of them stated that it was blinded. The other seven works did not provide information. In addition, 26 of the studies were randomized. Only ten results presented methodologies using only *Lactobacilli*; another 18 linked *Lactobacilli* with other beneficial microorganisms.

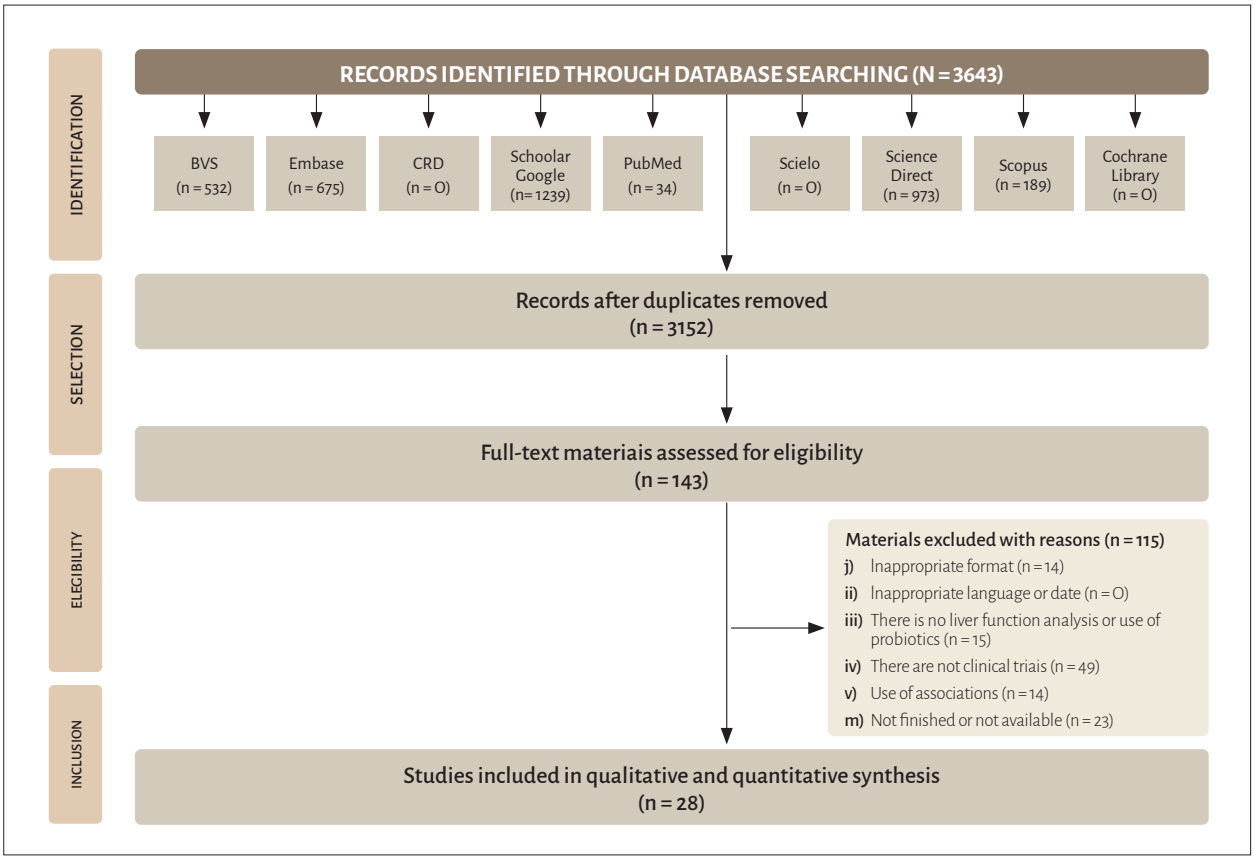
Concerning the place of the study, the obtained reports referred volunteers mainly from Asia (64,29%), followed by Europe (21,43%), Africa (10,71%), and Oceania (3,57%), without studies in America (Figure 2).

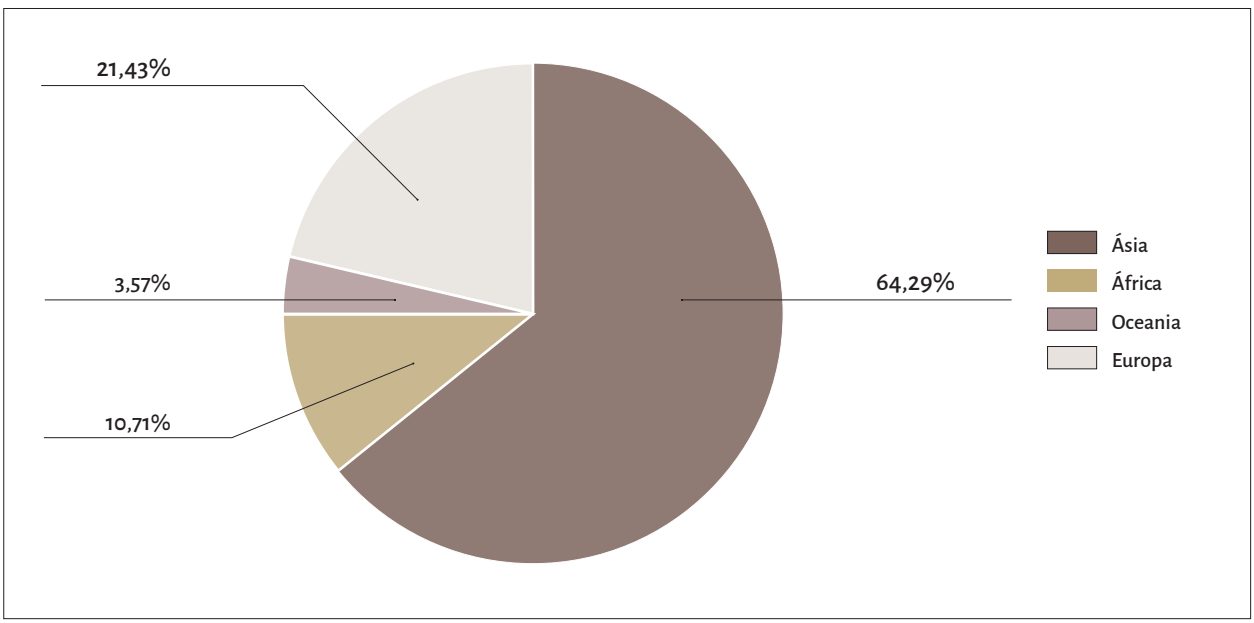
**Table 1.** Search strategy used in each database.

| Database | Search strategy |
|---|---|
| Google Scholar, Scopus and Science Direct - English | "Lactobacillus" AND "liver function" |
| Google Scholar, Scopus and Science Direct - Portuguese | "Lactobacillus" AND "função hepática" |
| PubMed - English | (("lactobacillus"[MeSH Terms] OR "lactobacillus"[All Fields]) AND (("liver"[MeSH Terms] OR "liver"[All Fields] OR "livers"[All Fields] OR "liver s"[All Fields]) AND ("functional"[All Fields] OR "functional s"[All Fields] OR "functionalities"[All Fields] OR "functionality"[All Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms]))) AND ((review[Filter]) AND (2011:2021[pdat])) |
| PubMed - Portuguese | (("lactobacillus"[MeSH Terms] OR "lactobacillus"[All Fields]) AND ("funcao"[All Fields] AND ("ranunculaceae"[MeSH Terms] OR "ranunculaceae"[All Fields] OR "hepatica"[All Fields]))) AND (review[Filter]) |
| Scielo and BVS - English | (Lactobacillus) AND (liver function) |
| Scielo and BVS - Portuguese | (Lactobacillus) AND (função hepática) |
| Cochrane Library - English | Lactobacillus in Title Abstract Keyword AND liver function in Title Abstract Keyword - (Word variations have been searched) |
| Cochrane Library - Portuguese | Lactobacillus in Title Abstract Keyword AND função hepática in Title Abstract Keyword - (Word variations have been searched) |
| CRD - English | ((Lactobacillus) AND (função hepática)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2011 TO 2021 |
| CRD - Portuguese | ((Lactobacillus) AND (função hepática)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA FROM 2011 TO 2021 |
| Embase - English | 'lactobacillus AND liver AND function AND [2011-2021]/py |
| Embase - Portuguese | 'lactobacillus AND função AND hepática AND [2011-2021]/py |

Adapted from PRISMA (14).

**Figure 1.** Information sources obtained, excluded, duplicated, and used from this bibliographic review

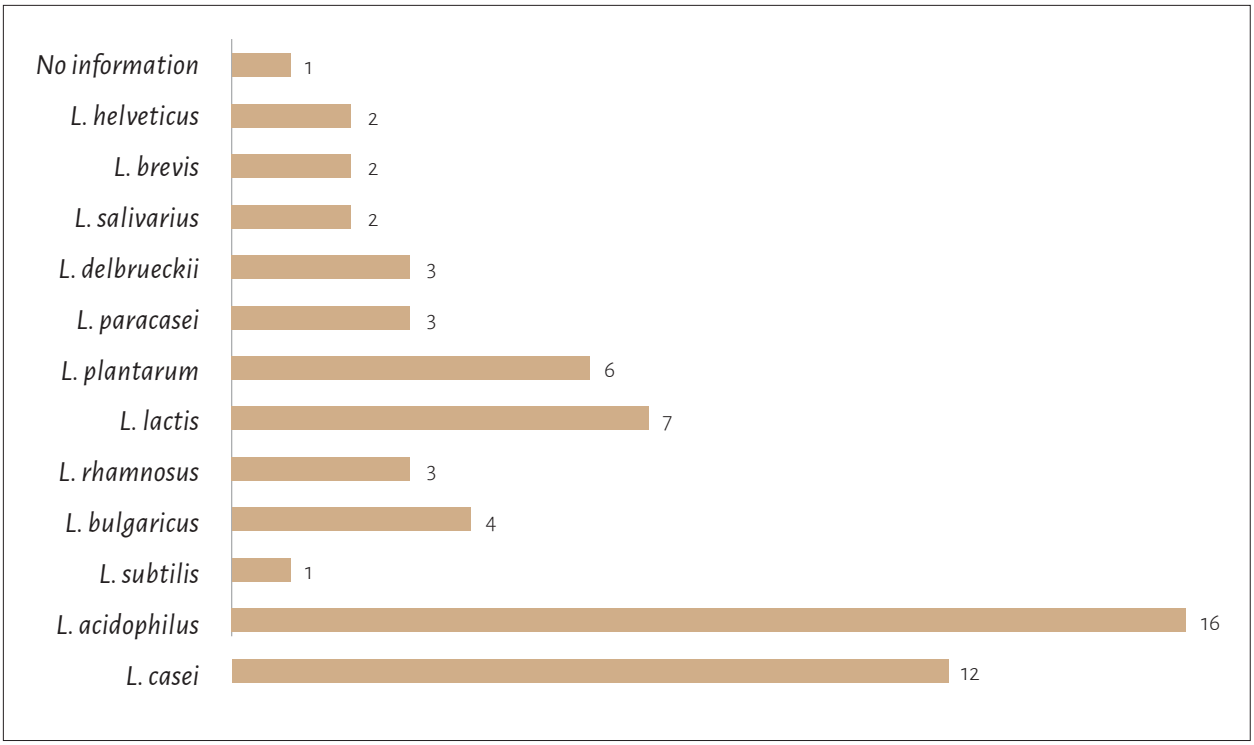



ASIA: SOUTH KOREA (7,14%), JAPAN (10,71%), MALAYSIA (7,14%), ISRAEL (3,57%), CHINA (14,29%), INDIA (10,71%), IRAN (3,57%), SRI LANKA (3,57%), IRAQ (3,57%); EUROPE: SPAIN (3,57%), ITALY (3,57%), POLAND (7,14%), AUSTRIA (3,57%), UNITED KINGDOM (3,57%); AFRICA: EGYPT (10,71%); OCEANIA: AUSTRALIA (3,57%).

Regarding the *Lactobacillus* species used by the researchers, *Lactobacillus acidophilus* stands out, with 16 citations in the methodologies, and *Lactobacillus casei*, with 12 citations (Figure 3). *Lactobacillus casei* is a popular species of study in probiotics due to its commercial value associated with improving capabilities in diarrhea, allergies, and obesity (15).

**Figure 3.** *Lactobacilli* species used in the methodologies of the articles that make up the collection of this review.




The results obtained by the different authors are shown in Table 2.

It is possible to observe through that most studies found improvement in some physiological parameters in the group treated with probiotics. Only four of twenty-eight studies found no significant differences between the control and treatment groups (8,17,26,32).

Pereg et al. (2011) and Firouzi et al. (2015) attribute the data without a significant difference to a low number of volunteers in the groups (8,26), as well as the short duration of the tests (26). However, other studies in this review found positive results even with a smaller population and a shorter term than the one used by them. The result obtained by Cox et al. (2014) can be explained by the fact that volunteers are healthy people without gastrointestinal, liver or metabolic tract comorbidities. However, such results demonstrated the safety of using probiotics in humans, given the absence of observed adverse effects (17). Finally, the study conducted by Yoshihisa et al. (2012) explained its results by a possible microbial death of the probiotics pashed in capsules over the weeks of study (32).

One study showed a negative effect of a long exposition of probiotics in liver transplants. There is a hypothesis not confirmed by the authors that the ingestion of probiotics can lead to the increase of some intestinal bacteria, such as *Lactobacillus* and *Bifidobacterium*, at the time of transplantation, which can facilitate intestinal lesions by the hepatitis C virus, the cause of death of patients in the study (22).

Regarding the outcomes evaluated by the researchers, liver function was the most estimated parameter, being present in 25 articles. In this regard, liver damage markers and proteins produced by this organ were evaluated. The reduction of inflammatory parameters was searched in 11 of the selected articles. Dysbiosis, on the other hand, was assessed in 10 studies, followed by intestinal permeability (6 papers). Metabolism alterations such as lipid profile and insulin resistance were evaluated in 6 studies. Finally, symptoms and/or exacerbations of hepatic encephalopathy were assessed to a lesser extent in only 5 articles.

**Hepatic diseases.** The volunteers who comprise the study groups of the present literature review often had some liver disease. Only two studies brought healthy volunteers to carry out their methodology (16,17).

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common hepatic disease around the world, characterized by fat in the liver tissue, necrosis, and increased inflammatory factors; on biochemical tests, there is a marked increase in liver enzymes. It is important to emphasize that there is no well-defined treatment for this pathology, and only lifestyle changes are indicated to reduce the percentage of body fat (5).

Still, other common hepatic pathologies are Alcoholic Hepatitis (AH) and Alcoholic Liver Cirrhosis (ALC). Such pathologies are caused, among other complex factors, by the interaction between alcohol metabolites, oxidants, and inflammatory species. Inflammation usually stems from microbial uncontrollability in the intestine. It happens due to the ability of alcohol to interfere with the intestinal barrier, promoting the translocation of pathogenic bacteria, mainly Gram-negative ones, to the hepatic portal circulation, culminating in the activation of defense cells in the liver through endotoxins, such as lipopolysaccharide (LPS), and, consequently, in liver fibrosis (1,18).

These conditions can lead to the so-called Hepatic Encephalopathy (HE), caused by the accumulation of nitrogenous substances (ammonia) resulting from the breakdown of proteins in the intestine by bacteria when the liver is unable to transform it into urea to be excreted in the urine, and this ends up crossing the blood-brain barrier and reaching the central nervous system. In addition, other substances produced by intestinal microorganisms, such as mercaptans, can lead to a worsening of the case through synergism with ammonia. In mild cases, in the so-called Minimal Hepatic Encephalopathy (MHE), the patient has neurological abnormalities, leading to difficulties in carrying out simple everyday tasks. This condition affects 30% to 84% of patients with liver cirrhosis (19).

**Mechanisms of action of probiotics.** It is well known that intestinal dysbiosis, an imbalance between the bacteria that make up the gut microbiota, is closely linked to a large number of diseases, such as diabetes, colorectal cancer, and even Alzheimer's. Therefore, the balance of intestinal microorganisms is one of the primary outcomes studied (10). One of the main actions attributed to probiotics is the promotion of a balanced intestinal microbiota by stimulating the growth of the anaerobic bacteria population and reducing pathogenic microorganisms (30). It is known that the uncontrolled increase of the natural microbiota, called Small Intestine Bacterial Overgrowth (SIBO), leads to peritonitis and other inflammation due to increased intestinal permeability; this occurs through the reduction of the junctions between the epithelial cells, essential for the maintenance of the integrity of the barrier (7,15,20).

The body's normal balance is maintained through the intestinal barrier; when there is a failure in this system, there is bacterial translocation to other organs and greater absorption of pro-inflammatory molecules, such as LPS.

**Table 2.** Synthesis of the methodology of the works of this literature review, as well as the main conclusions obtained by the authors. In the studies that opted for the use of more than one species of probiotic, all were administered together to the volunteers.

| Reference | Microorganism | Experimental Design | Results |
|---|---|---|---|
| Han et al., 2015 (1) | *Lactobacillus subtilis* and *Streptococcus faecium* | Group 01: 60 patients with AH, treated with 500 mg of probiotics three times a day for a week; Group 02: 57 patients with AH, with administration of placebo three times a day, for a week; | In the treated and placebo groups, there was a decrease in ALT, AST, γGT, TB, and PT levels, with no significant difference between them. There were no changes in the levels of protein and cholesterol. There was a decrease in the levels of LPS in the treated group, as well as TNF-α and pathogenic bacteria. |
| Aller et al., 2011 (5) | *Lactobacillus bulgaricus* and *Streptococcus thermophilus* | Group 01: 14 patients with NAFLD, treated with 500 million probiotics once a day for 3 months; Group 02: 14 patients with NAFLD, with administration of placebo (120 mg of starch) once a day for 3 months; | In the treated group, there was a decrease in ALT, AST and γGT levels. There were no changes in the inflammatory levels in either group (TNF-α and IL-6). |
| Vajro et al., 2011 (6) | *Lactobacillus rhamnosus* strain GG | Group 01: Obese pediatric patients with liver abnormalities, treated with 12 billion CFU of probiotics once daily for 8 weeks; Group 02: Obese children with liver abnormalities treated with placebo once a day for 8 weeks; | There was an improvement in ALT values in the treated group and in SIBO progression. |
| Mohamad Nor et al., 2021 (7) | *Lactobacillus acidophilus* BCMC 12,130 (107 mg), *L. casei* subsp *L. lactis* BCMC 12,451 (107 mg), *Bifidobacterium bifidum* BCMC 02290 (107 mg), *B. infantis* BCMC 02129 (107 mg) and *B. longum* BCMC 02120 (107 mg) | Group 01: 17 NAFLD patients treated with 30 billion CFU of probiotics twice a day for six months; Group 02: 22 NAFLD patients treated with placebo twice a day for six months; | There were no statistical differences between the treated and control groups regarding AST, ALT, γGT, fibrosis, and steatosis levels. However, the treated group was protected from the increased intestinal permeability observed in the control group. |
| Pereg et al., 2011 (8) | *Lactobacillus acidophilus, L. bulgaricus, Bifidobacterium bifidum*, and *Streptococcus thermophilus* | Group 01: 20 patients with CLC, treated with 2 x 1010 CFU of probiotics once a day for six months; Group 02: 15 patients with CLC, treated with placebo (non-fermentable wheat-based fibers) once a day for six months; | Between groups, there was no significant difference in plasma albumin, ALT, AST, bilirubin, creatinine, ammonia, and TP levels. |
| Elhawari and Emad, 2011 (9) | *Lactobacillus acidophilus* | Group 01: 100 HC patients treated with 100 million active probiotics three times a day for 2 weeks; Group 02: 48 healthy patients who did not receive anything; | There were no significant differences in serum bilirubin, ALT, and TP values. However, there was an improvement in HE parameters in the treated group. |
| Higashikawa et al., 2020(10) | *Lactobacillus plantarum* SN13T | Group 01: 11 patients with a slight increase in liver enzymes, treated with 1,2×1011 of live probiotics once a day for 16 weeks; Group 02: 10 patients with a slight increase in liver enzymes, treated with 1,2×1011 heat-killed probiotics once a day for 16 weeks; | There was a decrease in AST, ALT, and inflammatory parameters (TNF-α) in both groups and a beneficial modulation of the gut microbiota. There was no alteration of γGT. |
| Caiet al., 2020 (11) | Bifid Triple Viable: *Bifidobacterium*, *Lactobacillus* and *Enterococcus* | Group 01: 70 patients with NAFLD, treated with 1 g of probiotics twice a day, for 3 months + diets and physical exercises; Group 02: 70 patients with NAFLD, treated with diets and physical exercises for 3 months; | The group treated with probiotics had an improvement in the parameters of ALT, AST, γGT, as well as improvement in intestinal dysbiosis, lipid levels, NAFLD and insulin resistance profile. No significant changes in TB. |

| Reference | Microorganism | Experimental Design | Results |
|---|---|---|---|
| Xiong et al., 2021 (15) | Yakult (*L. casei* Shirota) | Group 01: 106 patients undergoing pharmacological treatment for tuberculosis, treated with 1 x 1010 CFU of probiotics once a day for 2 months;<br>Group 02: 114 patients undergoing pharmacological treatment for tuberculosis, treated with 1 x 1010 CFU of probiotics twice a day for 2 months;<br>Group 03: 105 patients undergoing pharmacological treatment against tuberculosis, without taking any probiotics or placebo; | There was an improvement in AST and TB values, as well as a decrease in inflammatory LPS and improvement in the intestinal microbiota. However, there were no differences between the groups regarding ALT, γGT and cases of hepatic encephalopathy. |
| Abd-Alwahab, and Fahad, 2018 (16) | Kefir ( *Lactobacillus helveticus*, *L. lactis*, *L. casei*, *Streptococcus cremoris*), *Streptococcus lacti*, *Kluyveromyces marxianus*, *Saccharomyces turicensis*, and *Pichia fermentans* | Group 01: 25 healthy volunteers who received 200 mL of tap water once a day for 21 days;<br>Group 02: 50 healthy volunteers, who received 200 mL of kefir fermented drink 5% (25 volunteers) and 7,5% (25 volunteers) once a day for 21 days; | The probiotic-treated group showed improvement in the lipid profile. There were no differences in AST and ALT values between groups. |
| Cox et al., 2014 (17) | *Bifidobacterium animalis* subsp. *lactis* Bl-04 (2,0 × 109 CFU), *Lactobacillus acidophilus* (5 × 109 UFC) NCFM and *B. animalis* subsp. *lactis* Bi-07 (5 × 109 CFU) | Group 01: 41 healthy volunteers who received probiotics once a day for 5 months;<br>Group 02: 45 healthy volunteers who received placebo once a day for 5 months; | There was no significant difference between groups regarding liver function parameters (ALT, AST, ALP, and TB) |
| Koga et al., 2013 (18) | Y400: *Lactobacillus casei* Shirota YIT 9029 | Group 01: 18 patients with compensated ALC treated with 40 billion CFU of probiotics twice a day for two weeks;<br>Group 02: 19 patients with compensated ALC, with the administration of placebo (lactic acid) twice a day for two weeks; | Both groups had no changes in ALT, AST, γGT, TB and ferritin levels. However, the treated group had a higher level of liver proteins (transthyretin). Furthermore, there was improvement in inflammatory parameters (CRP) and intestinal dysbiosis. |
| Ziada et al., 2013 (19) | *L. acidophilus* | Group 01: 24 patients with cirrhosis and MHE, treated with 30-60 mL of lactulose once a day for 1 month;<br>Group 02: 26 patients with cirrhosis and MHE, treated with 1x106 of probiotics three times a day for 1 month;<br>Group 03: 25 patients with cirrhosis and MHE as a control group; | In the group treated with probiotics and lactulose, there was an 80% decrease in the probability of developing evident HE, with improvement in psychomotor tests and a reduction in ammonia and glutamine levels, due to the change in the intestinal microbiota. However, the probiotics group had better tolerability and treatment adherence. |
| Kwak et al., 2014 (20) | *Bifidobacterium lactis* (KCTC 11904BP), *B. bifidum* (KCTC 12199BP), *B. longum* (KCTC 12200BP), *Lactobacillus acidophilus* (KCTC 11906BP), *L. rhamnosus* (KCTC 12202BP), and *Streptococcus thermophilus* (KCTC 11870BP) | Group 01: 25 patients with CLD, treated with 5 × 109 viable cells of probiotics twice a day for four weeks;<br>Group 02: 25 patients with CLD, treated with placebo twice a day for four weeks; | In the treated group, there was an improvement in the SIBO. There was no difference between the groups in terms of improvement in intestinal permeability, nor in the values of AST, ALT, TB, TP. |
| Grat et al., 2017 (21); and Grat et al., 2020 (22) | ProBacti 4 Enteric: *Lactococcus lactis* PB411 (50,0%), *L. casei* PB121 (25,0%), *Lactobacillus acidophilus* PB111 (12,5%), and *Bifidobacterium bifidum* PB211 | Group 01: 26 patients with pre-transplant HC, treated with 3 x 109 CFU of probiotics once a day from two to ten weeks;<br>Group 02: 29 patients with pre-transplantation HC, treated with placebo once a day for two to ten weeks; | In the treated group, there was a reduction in bilirubin levels, AST, and ALT, as well as an improvement in dysbiosis and postoperative infection rates. There was no difference in labor, hospitalization, or time of antimicrobial use.<br>After a 5-year follow-up of patients, it was noted that prolonged administration of probiotics prior to liver transplantation has a negative effect on long-term allograft function. |

| Reference | Microorganism | Experimental Design | Results |
|---|---|---|---|
| Lunia et al., 2014 (23) | *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*, and *Streptococcus thermophilus* | Group 01: 86 HC patients treated with 100 billion CFU of probiotics three times a day for 3 months;<br>Group 02: 74 HC patients who did not receive anything; | There was a decrease in HE occurrence in the probiotic-treated group and in SIBO and ammonia levels. |
| Asemi et al., 2015 (24) | *Lactobacillus acidophilus* (2×109 UFC), *L. casei* (7× 109 UFC), *L. rhamnosus* (1,5×109 UFC), *L. bulgaricus* (2×108 UFC), *Bifidobacterium breve* (2×<br>1010 UFC), *B. longum* (7×109 UFC), *Streptococcus thermophilus* (1,5×109 CFU) | Group 01: 28 patients with DM2, treated with probiotics once a day for 8 weeks;<br>Group 02: 30 patients with DM2, treated with placebo once a day for 8 weeks; | In the treated group, there was an increase in calcium levels and a reduction in ALT. There was no change in other parameters of ions, TB, ALP, and AST. |
| Duseja et al., 2019 (25) | IVOMIXX, VISBIOME and DESIMONE: *Lactobacillus. paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* subsp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731 | Group 01: 17 patients with NAFLD, treated with 675 billion CFU of probiotics once a day for 12 months + physical exercises;<br>Group 02: 13 patients with NAFLD, treated with placebo (microcrystalline cellulose) once a day for 12 months + physical exercises; | The treated group had improvement in liver histology, as well as ALT levels and inflammatory markers (TNF-α, IL-1β, IL-6). There was no difference in terms of insulin resistance. |
| Firouzi et al., 2015 (26) | Hexbio: *Lactobacillus acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *Bifidobacterium longum* and *B. infantis* | Group 01: 48 patients with DM2, treated with 6×1010 CFU of probiotics once a day for 12 weeks;<br>Group 02: 53 patients with DM2, treated with placebo once a day for 12 weeks; | There were no significant differences in ALP, AST, ALT, TB, and albumin values, only a reduction in total proteins. |
| Horvath et al., 2016 (27) | *Bifidobacterium bifidum* W23, *B. lactis* W52, *Lactobacillus salivarius* W24, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *Lactococcus lactis* W19 and *L. lactis* W5 | Group 01: 44 patients with HC, treated with 15 x 109 of CFU of probiotics once a day for 6 months;<br>Group 02: 36 patients with HC, treated with placebo once a day for 6 months; | There was an increase in resting neutrophil bursts in the treated group compared to the control group. However, there were no differences in neutrophil phagocytosis, endotoxin load, intestinal permeability, or inflammatory markers. The liver function had a slight improvement in the treated group. |
| Li et al., 2021 (28) | *Lactobacillus casei* Shirota | Group 01: 46 patients with ALD, treated with placebo once a day for 2 months;<br>Group 02: 58 patients with ALD, treated with 10 billion probiotics once a day for 2 months;<br>Group 03: 54 patients with ALD, treated with 10 billion probiotics twice a day for 2 months;<br>Group 04: 20 healthy patients who received no treatment; | There was a decrease in ALT, AST, TB, γGT levels, and lipid profile in the groups treated with probiotics. Furthermore, there was an improvement in the microbiota, intestinal permeability, and anti-inflammatory factors (IL-10). |
| Liu et al., 2015 (29) | *Lactobacillus plantarum*, *L. acidophilus* and *Bifidobacterium longum* | Group 01: 66 patients with CC, treated with 2,6 × 1014 of CFU of probiotics once daily for 16 days (6 preoperative days and 10 postoperative days);<br>Group 02: 68 patients with CC, treated with placebo (maltodextrin) once a day for 16 days (6 days preoperatively and 10 days postoperatively); | There was a decrease in ALT, AST, and plasma endotoxin levels in the treated group. In addition, there was an improvement in intestinal permeability and in the levels of postoperative infection. |
| Monem, 2017 (30) | *Lactobacillus acidophilus* | Group 01: 15 patients with NASH, treated with 2 billion probiotics three times a day for 1 month;<br>Group 02: 15 patients with NASH who received nothing; | ALT and AST levels decreased in the treated group. There was no change in the parameters of albumin, serum bilirubin, and proteins. |

| Reference | Microorganism | Experimental Design | Results |
|---|---|---|---|
| Rodrigo et al., 2021 (31) | Bio-Kult 14: *Bacillus subtilis* PXN 21, *B. bifidum* PXN 23, *B. breve* PXN 25, *B. infantis* PXN 27, *B. longum* PXN 30, *Lactobcillus acidophilus* PXN 35, *L. delbrueckii* ssp. *bulgaricus* PXN 39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57, *Lactococcus lactis* ssp. *lactis* PXN 63, *Streptococcus thermophilus* PXN 66 | Group 01: 43 pediatric patients with NAFLD/NASH, treated with one (under 12 years old) or two capsules (over 12 years old) containing 2x109 CFU of probiotics once a day + diet and physical exercises for 6 months;<br>Group 02: 41 pediatric patients with NAFLD/NASH, treated with one or two capsules containing placebo (microcrystalline cellulose) once a day + diet and physical exercises for 6 months; | Compared to the control group, there was no improvement in AST, ALT, and ALP levels, as well as in the lipid profile and insulin resistance in the treated group. There was improvement only in liver fat levels. |
| Yoshihisa et al., 2012 (32) | *Lactobacillus brevis* SBC8803 | Group 01: 22 patients with increased γGT, treated with 3,3 × 109 CFU of probiotics twelve times a day for 8 weeks;<br>Group 02: 23 patients with increased γGT, treated with placebo twelve times a day for 8 weeks; | There was an improvement in γGT levels after 4 weeks of treatment. Still, there was no significant difference in ALT, AST, and γGT levels after 8 weeks of treatment. |
| Dhiman et al., 2014 (33) | *Lactobacillus paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, *L. delbrueckii* ssp. *bulgaricus* DSM 24734, *Bifidobacterium longum* DSM 24736, *B. infantis* DSM 24737, *B. breve* DSM 24732, and *Streptococcus thermophilus* DSM 24731 | Group 01: 16 patients with HC who recently recovered from an episode of HE, treated with 9x1011 CFU of probiotics once a day for 6 months;<br>Group 02: 13 patients with HC who recently recovered from an episode of HE, treated with placebo (corn flour) once a day for 6 months; | Patients in the treated group were less likely to be hospitalized due to HE episodes, decreased inflammatory factors (TNF-α, IL1β, and IL6), and improved liver function. There were no significant changes in ammonia levels between both groups. |
| Macnaughtan et al., 2020 (34) | Yakult Europe: *Lactobacillus casei* Shirota | Group 01: 33 patients with stable HC, who received 6,5 × 109 CFU of probiotics three times a day for 6 months;<br>Group 02: 35 patients with stable HC, who received placebo three times a day for 6 months; | There was an improvement in neutrophil activity in patients with a previous low in the treated group and a decrease in some inflammatory cytokines. There was no difference in the rate of hospitalization, decompensation, or infection between the groups and in liver function parameters, intestinal permeability, and endotoxins. |

AH: ALCOHOLIC HEPATITIS; ALD: ALCOHOLIC LIVER DISEASE; ALP: ALKALINE PHOSPHATASE; ALT: ALANINE AMINOTRANSFERASE ; AST: ASPARTATE AMINOTRANSFERASE; CLD: CHRONIC LIVER; DISEASE; CRP: C-REACTIVE PROTEIN; CFU: COLONY FORMING UNIT; DM: DIABETES MELLITUS; HC: HEPATIC CIRRHOSIS ; HE: HEPATIC ENCEPHALOPATHY; IL: INTERLEUKIN; LPS: LIPOPOLYSACCHARIDE; MHE: MINIMAL HEPATIC ENCEPHALOPATHY; NAFLD: NON-ALCOHOLIC FATTY LIVER DISEASE; NASH: NON-ALCOHOLIC STEATOHEPATITIS; PT: PROTHROMBIN; TB: TOTAL BILIRUBIN; TNF-A: TUMOR NECROSIS FACTOR –ALPHA; SIBO: SMALL INTESTINAL BACTERIAL OVERGROWTH; ГGT: GAMMA-GLUTAMYL TRANSFERASE TIME;

The endotoxemia caused by this condition is especially apparent in the liver, as it receives blood directly from the intestine. Although the liver has processes to detoxify itself, the same does not occur in patients with pre-existing liver problems, culminating in several liver pathologies due to the accumulation of pro-inflammatory molecules that damage hepatocytes and can lead to organ dysfunction, fibrosis (31), triggering or aggravating pre-existing conditions, such as cholestasis. Other pathologies associated with bacterial translocation are hepatic encephalopathy, steatosis, hepatic fibrosis, and hepatorenal syndrome (7,15,20).

Some studies in this review demonstrated the ability of *Lactobacilli* to restore the amount of *Clostridium coccoides*, *Clostridium leptum,* and *Bacterioides fragilis*, as well as to reduce levels of Enterobacteriaceae, which are harmful when in imbalance (18). Furthermore, increased levels of *Bacterioides* species are known to positively affect the gastrointestinal tract (21). Kwak et al. (2014) managed to reverse SIBO in treated patients by decreasing hydrogen-producing bacteria (20). As a result, there was a decrease in urease-producing bacteria, such as *Klebsiella* and *Proteus* species, culminating in lower production and absorption of ammonia, which is toxic to the brain. In addition,

the ability of probiotics to decrease inflammation and oxidative stress in hepatocytes by improving ammonia clearance is noted (8,19).

Concerning intestinal permeability, the probable cause of its decrease in the presence of probiotics is the ability these microorganisms have to increase the viability of the intestinal epithelium through essential nutrients for the viability of these cells (19). Literature data states that supplementation with commensal bacteria, such as *Lactobacillus*, *Bifidobacterium,* and *Streptococcus*, can assist intestinal permeability and decrease bacterial translocation. It can be observed in the study carried out by Xiong et al. (2021), who demonstrated the ability of supplementation with *L. casei* to decrease Gram-negative Bacterioidetes species with a role in LPS synthesis and improve intestinal permeability. In addition, there was an increase in the number of beneficial bacteria in the intestines of treated patients (15).

LPS molecules, which are harmful to the body, have different ways of harming the liver. They can reduce the production of bile acid transporters, culminating in their intracellular accumulation in hepatocytes and, consequently, cell death and necrosis. In addition, LPS is responsible for increasing hepatic oxidative stress, as it induces the production of enzymes that produce reactive oxygen species (ROS), such as CYP2E1 (15).

Furthermore, supplementation with probiotics has effects on liver function. Generally, liver health is characterized by simple biochemical tests that quantify liver enzymes such as ALT, AST, ALP, and γGT. As an example, it can be mentioned that the increase in ALP and total bilirubin is linked to liver damage, such as cholestasis (15); still, elevated ALT is a marker of hepatocyte damage (24). Currently, more attention has been given to quantifying γGT, a molecule in hepatocytes and bile cells, which is a biomarker of alcohol-induced liver damage. Its increase is associated with damage from oxidant species, a risk factor for cardiovascular disease, diabetes, and non-alcoholic steatohepatitis (32). The decrease in these parameters, usually exacerbated in liver pathologies, is a positive factor in treating patients.

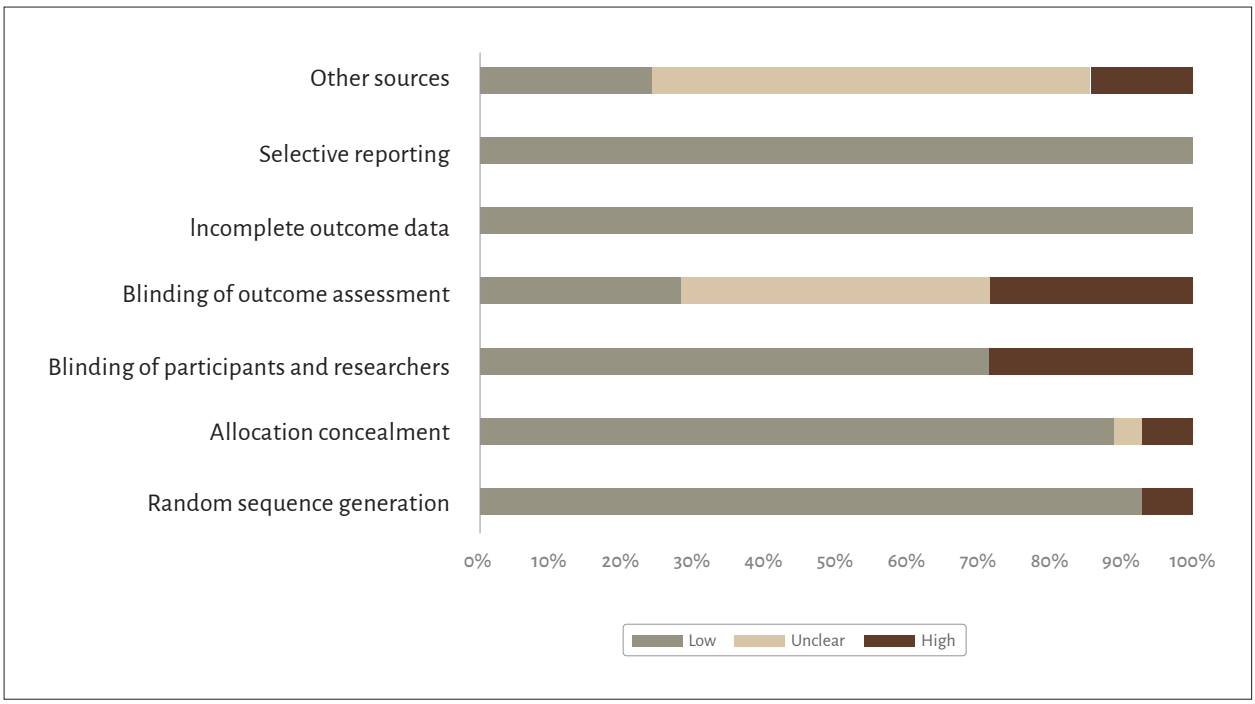
Some studies in the present review presented the improvement of enzymatic parameters with ingesting probiotics, such as *Lactobacilli*. As an example, the work conducted by Aller et al. (2011) can be cited. There was a decrease in ALT enzymes (67,7 IU/L before treatment and 60,4 IU/L after treatment), AST (41,3 IU/L before treatment and 35.6 IU/L L after treatment), and γGT (118,2 IU/L before treatment and 107,7 IU/L after treatment) (5). Vajro et al. (2011) found a substantial decrease in ALT levels (70,3 IU/L before treatment and 40.1 IU/L after treatment) (6). The data obtained by Cai et al. (2020) demonstrate a reduction in ALT (76,38 IU/L before treatment *versus* 34,18 IU/L after treatment), AST (57,23 IU/L before treatment; 32,49 IU/L after treatment), and γGT (30,95 IU/L before treatment; 15,17 IU/L after treatment) (11).

Another way of measuring the outcome of treatment against liver diseases is by quantifying proteins produced by the liver. The increase in production indicates good organ functioning, maintaining usual functions, and being important indicators of nutritional parameters. Among them, transthyretin, an important nutritional factor linked to the metabolism of iron, thyroxine, and retinol, synthesized by hepatocytes, can be mentioned. In addition, other proteins synthesized by the liver are albumin and transferrin (18).

Koga et al. (2013) demonstrated the capacity of consumed probiotics to promote the production of proteins by liver cells; this leads to an improvement in the osmotic pressure of the blood, as well as aiding in the transport of small molecules throughout the body (18).

In some studies, probiotics' consumption reduced inflammatory cytokines' expression. Information from the literature affirms that this occurs through altering the signaling of such communication molecules (25). This decrease in the exposure of liver cells to inflammatory mediators, endotoxins, and oxidative stress leads to an improvement in liver function, as observed in many of the studies presented here (9). Among the inflammatory parameters studied, TNF-α stands out for its role in insulin resistance and the production of oxidant factors, as well as in NAFLD and SHNA; when its levels are high, there is an increase in the severity of these diseases (10,30). Because it is important, it is generally targeted in treating cirrhosis using Infliximab (1). Still, other important cytokines have their production minimized by treatment with probiotics, such as Interleukin 1, 6, and 8 (18).

**Figure 4.** Graphically representation of risk of bias.




Another outcome observed in some studies was the improvement in the lipid profile of patients treated with probiotics. The translocation of pathogenic bacterial molecules can affect the metabolism of lipids and glucose and interfere with insulin resistance, increasing it. *Lactobacilli* intervene positively in these cases, as their metabolites can inhibit enzymes involved in the production of lipids, such as cholesterol synthetase, in addition to decreasing intestinal absorption of cholesterol. Finally, it is known that beneficial bacteria can also increase the excretion of cholesterol from bile salts in the feces (11), and lowering intestinal pH may increase cholesterol precipitation (16).

Five studies of the present bibliographic review studied such parameters of lipid metabolism. Three of them found significant improvement (11,16,28). In contrast, two others did not observe statistical differences in the improvement of the lipid profile between the probiotic-treated group and the control group (1,31).

**Adverse effects.** In all studies of the present literature review, no serious adverse effects were observed, proving the safety of these probiotics, even over long periods of treatment (19). It is even more interesting when it is observed that some drugs used in cases of liver dysfunction, such as lactulose, are commonly associated with constant adverse effects, such as flatulence, diarrhea, nausea, and abdominal pain (19,23).

**Limitations.** Although the results obtained by the studies of this review have been promising in several aspects in improving liver function in sick individuals, it should be noted that the methodological procedure of each of the authors was very different from each other.

The main variations observed were in the species of *Lactobacilli* used and their association with other microorganisms, in addition to the amount used and the chosen dosage regimen, making the comparison of results difficult and the impossibility of reaching definitive conclusions about the use of probiotics in liver diseases.

Another point that makes the comparison between the methodologies of the studies complex is the way of expressing the amount of probiotics administered. Most studies chose to define the amount in CFU (6,8,15,17,18,21-27,29,31-34). Some works have provided such information in

milligrams (1), grams (11), and milliliters (16). Only one of them had both forms of identification (7). Finally, some authors brought only the numerical quantity without a descriptive term (5,9,10,19,28,30). One study highlighted the number of microorganisms associated with the term "viable cells" (20).

Another crucial point of wide variation across studies was the duration of probiotic treatment. Some authors obtained results after a few weeks of ingestion of microorganisms, while others followed their patients for a year.

Therefore, the presented information here should not be generalized to other types of formulations containing different types, amounts, and associations of probiotics and other manufacturing processes of the consumed products.

**Risk of bias.** The result of the risk of bias analysis, carried out using the Cochrane Risk of Bias Tool, is shown in Figure 4. It is noted that the blinding of participants, researchers, and the outcome evaluation were the points with the highest number of high risks of bias. Regarding other sources of bias, because it is a broad topic, uncertainty appeared in a large percentage, mostly due to the low number of study participants.

## CONCLUSION

The clinical studies obtained in this literature review corroborated that the consumption of probiotics containing *Lactobacilli*, isolated or in association with other symbiotic microorganisms, improves liver function parameters in patients with pathologies of this organ, as well as other factors related to the quality of life. Little difference was seen in healthy volunteers who received probiotics compared to the placebo group. Furthermore, they were well tolerated by the vast majority of patients, with few adverse effects, which, when observed, were light and tolerable. It makes probiotics containing *Lactobacillus* species a natural alternative for treating patients with liver disorders, improving the quality of life, even in long-term treatments.

The mechanisms associated with *Lactobacilli* that help to explain their action are diverse, including improvement of intestinal dysbiosis, promoting balance between microbiota species, decreased permeability of the intestine, and, consequently, bacterial translocation through cell membrane stability. In addition, there was a reduction in the inflammatory response profiles, with a decrease in the production of pro-inflammatory cytokines.

Although the data found in this review are promising, more studies are needed with well-established, double-blind methodologies, with a greater range of studied population, to clarify the real benefits in the liver function of using probiotics with Lactobacilli species.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests involved in this work.

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