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Review Article

Effect of treatment with probiotics in the reduction of altered levels of the lipid profile in humans and rats: a systematic review

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ABSTRACT

Introduction: Evidence suggests that the use of probiotics can prevent or help in the treatment of diseases such as obesity, acute infectious diarrhea, irritable bowel syndrome, liver problems, and the correction of hyperlipidemia, whether in total cholesterol, c-HDL, c-LDL or triglycerides. Probiotic strains have been studied so that with various mechanisms they can decrease lipid levels in children, adults and rats. **Objective:** To demonstrate the lipid-lowering effect of some probiotic strains tested in humans and rats, by compiling research that supports it. **Methods:** A search was carried out for articles with a year of publication between 2013 and 2023, experimental, observational and cohort studies published in English, full text available and analysis of the decrease in some lipid profile marker due to the use of probiotics. The MESH terms and the Boolean operators used for the search were "probiotics, lipid-lowering, children; Adults; rats and lipid profile". Data sources: the databases used were PubMed, Google Scholar, Elsevier, Clinical Key, and ScienceDirect. **Results:** From a total of 2150 articles, 30 were included. After the analysis of the selected articles, the results reveal that probiotics have a beneficial effect on the lipid profile by 25,01%. Total cholesterol level was reduced by 16,65%, c-LDL 32,02% and c-HDL was raised by 21,71%. **Conclusion:** Supplementation with specific strains of probiotics has a lipid-lowering effect, it especially reduces hypercholesterolemia through various mechanisms, but more studies are required to determine the dosage and treatment time.

Key words: probiotics; lipid-lowering; children; adults; rats and lipid profile.

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RESUMEN

Introducción: Las evidencias sugieren que el uso de probióticos puede prevenir o ayudar en el tratamiento de enfermedades como la obesidad, diarrea aguda infecciosa, síndrome de intestino irritable, problemas hepáticos y la corrección de la hiperlipidemia ya sea del colesterol total, HDL-C, LDL-C o triglicéridos. Se han estudiado cepas probióticas que con diversos mecanismos pueden disminuir los niveles lipídicos en niños, adultos y ratas. **Objetivo:** Evidenciar el efecto hipolipemiante de algunas cepas probióticas probadas en humanos y ratas, recopilando investigacionesqueloavalen. **Métodos:** Se realizó una búsqueda de artículos con año de publicación entre 2013 a 2023, estudios experimentales, observacionales y de cohortes publicados en inglés, texto completo disponible y análisis de la disminución de algún marcador del perfil de lípidos por el uso de probióticos. Los términos MESH y los operadores booleanos utilizados para la búsqueda fueron "probióticos, hipolipemiante, niños; adultos; ratas y perfil de lípidos". Fuentes de datos: las bases de datos utilizadas fueron PubMed, Google Scholar, Elsevier, Clinical Key y ScienceDirect. **Resultados:** De 2150 artículos, 30 fueron incluidos. Después del análisis de los artículos seleccionados, los resultados revelan que los probióticos tienen un efecto benéfico sobre el perfil de lípidos en un 25,01%. Se redujo 16,65% el nivel de colesterol total, 32,02% LDL-C y elevando el HDL-C un 21,71%. **Conclusión:** La suplementación con cepas específicas de probióticos tiene efecto hipolipemiante, en especial es reductor de la hipercolesterolemia a través de diversos mecanismos, pero se requieren más estudios para determinar la dosificación y el tiempo de tratamiento.

Palabras clave: probióticos; hipolipemiante; niños; adultos; ratas; perfil de lípidos.

INTRODUCTION

Dyslipidemias are alterations of lipid metabolism, they are associated with atherosclerotic process and ischemic processes. The cardiovascular risk to which each of them is predisposed is different, depending on the type of lipoprotein that is altered and its concentration, total cholesterol levels and serum triglycerides.[1] The National Health and Nutrition Survey (ENSANUT) 2020, in Mexico, states that the most common dyslipidemias in adults were hypercholesterolemia (26,1%), hypertriglyceridemia (49%) and low-density cholesterol (c-HDL) level (28,2%).[2] The objective of the treatments for alterations in the lipid profile is largely focused on reducing the levels of total cholesterol, low-density lipoproteins (c-LDL), elevated triglyceride values and increasing high-density lipoproteins (c-HDL) to prevent the stiffness of the arteries due to the generation of atherogenic plaque, cerebrovascular accidents that have poor prognoses, increasing morbidity and mortality.[3]

Cholesterol is part of all steroid hormones and vitamin D analogues, therefore, a deficiency of cholesterol in the circulation can result in an inability to distribute vitamins K and E to vital organs, causing severe consequences. In contrast, hypercholesterolemia, or cholesterol buildup, is caused by excess dietary cholesterol or a genetic abnormality and can result in cardiovascular disease and death.[4] Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid storage, steroid hormone production, and bile acid formation. Lipoproteins are categorized based on their density, and c-LDL, c-HDL, IDL, VLDL, and chylomicrons can be isolated by ultracentrifugation.[5] Triglycerides have a transcendental role in the energy reserve of our organism, the normal value of serum triglycerides should be less than 150 mg/dL, since above this figure alterations are observed in the increase of c-LDL, that are related to atherogenic risk.[6] The 2018 Guidelines of various associations such as the American Heart Association (AHA), American Diabetes Association (ADA), Expert Panel on Cholesterol Levels in Children for cholesterol management mentions acceptable ranges for total cholesterol (TC) concentrations > 200 mg/dl, c-LDL <130 mg/dl, c-HDL > 60 mg/dl and TG < 150 mg/dl in adults and in children TC > 170 mg/dl, c-LDL <110 mg/dl, c-HDL > 45 mg/dl, TG < 75 mg/ dl (0-9 years) and < 90 mg/ dl (10-19 years).[7]

Probiotics in the reduction of altered levels of the lipid profile

Probiotics are defined as those live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the host. They are considered safe for human consumption. The most researched and used probiotics in the clinical area include bacteria of the following genera: *Lactobacillus, Lactococcus, Leuconostoc, Pediococcus, Propionibacterium, Bifidobacterium, Bacillus, Streptococcus, Enterococcus, Escherichia coli* and yeasts of the genus *Saccharomyces*.[8] According to Lye *et al*. (2010), some bacterial strains or consortia have been shown to reduce cholesterol, lipoprotein, and triglyceride levels.[9] There are different

mechanisms proposed to explain the reduction in c-LDL, in relation to the intake of probiotics, which include:

1. Deconjugation of bile acids, by the production of enzymes such as bile salt hydrolase, which interfere with the ability of cholesterol to be incorporated into mixed micelles, thus reducing its absorption.

2. Interference of the bioavailability of cholesterol in the small intestine through the absorption of cholesterol in bacterial cell walls.

3. Production of short-chain fatty acids through colonic fermentation of indigestible carbohydrates, which can inhibit cholesterol synthesis and suppress the release of free fatty acids from adipose deposits, a substrate for triglyceride synthesis.[10]

The cholesterol-lowering ability of probiotics has been extensively reviewed through various clinical trials. Several mechanisms have been proposed, but one of the most accepted is the ability to deconjugate bile by the production of bile salt hydrolase (BSH). Deconjugated bile salts are less reabsorbed in the intestines compared to conjugated salts, resulting in greater fecal excretion because they are more hydrophobic. Cholesterol, being the precursor of bile salts, is used to produce new bile salts, resulting in a decrease in serum concentrations.[11]

To prove that probiotics do not cause harm to the consumer, *in vitro* tests are necessary, followed by preclinical tests in animal models such as rodents and finally in humans.[12] Rats are a type of mammals that are used in research due to their physical and genetic characteristics similar to humans, in addition, their size is small, they are accessible, they adapt to all habitats, among others.[13] Experimentation with rodents continues to be the most used in biomedical research, its purpose is to obtain the greater good through protocols and methodologies reviewed, approved and supervised by ethics committees to guarantee their well-being from birth.[14]

The objective of this review is to determine the effect that some probiotic strains have on the reduction in abnormal levels of total cholesterol, triglycerides and c-LDL, as well as the increase in serum c-HDL.

METHODS

Literature search

This review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[15]

Search strategy

The databases required to search for scientific articles were PubMed, Google Scholar, Elsevier, ClinicalKey, and Science-Direct. The MESH terms and the Boolean operators used for the search were “probiotics”, “lipid-lowering”, “children”, “adults”, “rats”, “lipid profile”, studies published in English and Spanish.

Eligibility criteria

All research articles with a year of publication between 2013 and 2023, experimental, observational, and cohort studies published in English and Spanish. The degree of efficacy of some probiotic strains on markers including the lipid profile (TC, c-HDL, c-LDL, and triglycerides) was determined. In addition, the inclusion of the use of probiotics in patients with dyslipidemia is proposed, since conventional treatment includes only drugs and eating plans to reach normal levels of lipid markers.

Study selection

Article records were individually recognized and identified by three investigators and, if necessary, decisions to include or not include a record were made by consent and agreement between them.

Quality assessment

One of the researchers performed the evaluation of the records using the Microsoft Excel data tool. Investigators had full access to all registration, evaluation, and data extraction spreadsheets.

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RESULTS

The schematic representation for the selection of the articles is found in Figure 1. A total of 2150 articles were found, then a debugging was carried out to eliminate some duplicates, leaving 1157, also some were excluded after reviewing the abstracts. In addition, an evaluation of the complete contents of the remaining 126 articles was carried out. Subsequently, 21 were excluded for not being released, 105 for not including the necessary terms and 75 for not expressing the results clearly. Finally, the articles included in the review are 30. Table 1 shows the summary of those selected.

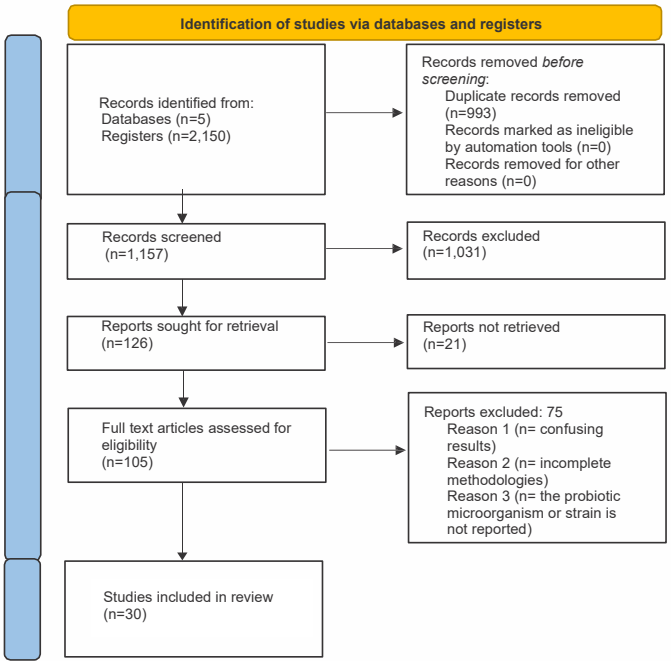

Figure 1. PRISMA flow chart. Represents the bibliographic search strategy for this systematic review.

Table 1. Summary of the results and main findings in the 30 studies included in this systematic review

	Author	Year	Country	Population	Study duration	Results
Articles on children						
1	Karyana I.P.G., *et al.*,[16]	2022	Indonesia	N=52 obese patients. Group 1: Treatment with probiotics (*Streptococcus thermophilus*, *Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium bifidum*) and group 2: placebo	8 weeks	Group 1: total cholesterol decreased by 22.6 mg/dL, c-LDL decreased by 16.9 mg/dL, TG decreased by 30.8 mg/dL, and c-HDL increased by 1.4 mg/dL.
2	Fortes PM, *et al.*,[17]	2020	Brazil	N=12 patients with nephrotic syndrome, 2 groups Grupo 1: *Lactobacillus plantarum*, cepa Lp-G18 2,5 x 10^9 CFU/ capsule Grupo 2: placebo	12 weeks	Group 1: average TC decrease of 41.5 mg/dL and TG decreased by 6.0 mg/dL. Group 2: TC increased (8.0 mg/dL), TG increased 49.5 mg/dL.

3	Guardamagna, *et al.*,[18]	2014	Italy	N=38 children with dyslipidemia (2 groups). Group 1 with placebo, group 2 treatment with probiotics (*B. animalis* subspecies *lactis* MB 2409, *B. bifidum* MB 109B, and *B. longum* subspecies longum BL04)	12 weeks	In the group treated with probiotics, they reduced TC by 3.4% and c-LDL by 3.8%.
Articles on adults						
4	AkbariRad M, *et al.*,[19]	2023	Iran	N=70 prediabetic patients. Group 1: Supplementation with Lactocare probiotics (*Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus termófilos* with fructooligosaccharide as a prebiotic) and group 2: Placebo.	12 weeks	Group 1: c-LDL and TG levels were reduced (2.61% and 11%, respectively) and the serum concentration of c-HDL increased by 8.68%
5	Wang S, *et al.*,[20]	2022	China	N= 365 patients (4 groups) Group 1: probiotics* + Berberine (BBR); group 2: probiotics* + placebo; group 3: BBR + placebo and group 4: placebo + placebo. **Bifidobacterium longum* CGMCC No. 2107; *Bifidobacterium breve*CGMCC No. 6402; *Lactococcus gasseri* CGMCC No. 10758; *Lactobacillus rhamnosus* CNCM I-4474; *Lactobacillus salivarius* CGMCC No. 6403; *Lactobacillus crispatus* CGMCC No. 6406; *Lactobacillus plantarum*; CGMCC No. 1258; *Lactobacillus fermentum* CGMCC No. 6407; and *Lactobacillus casei* CNCM I-4458.	12 weeks	Group 2: reduction TCp= 7.83%, pc-LDL = 21.4% Group 4: TCp reduction = 6.88%, pc-LDL= 17.28%
6	Guerrero-Bonmatty R, *et al.*,[21]	2021	Spain	N=39 patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactoplantibacillus plantarum* strains (CECT7527, CECT7528, and CECT7529) combined with yeast rice extracts.	12 weeks	The use of probiotics in combination with rice yeast extract reduced TC (31.4 mg/dL), in addition to a decrease in serum c-LDL (23.6 mg/dL).

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7	Trotter RE, *et al.*,[22]	2020	EE.UU.	N= 88 humans (4 groups). Group1: Placebo + maltodextrin; group 2: *Bifidobacterium lactis* cepa BL04; group 3: PreforPro bacteriophages; group 4: *Bacillus subtilis* strain DE111.	4 weeks	Group 3: reduction TC= 2.27%, c-LDL = 0.48%. Group 4: reduction TC= 4.64%, c-LDL = 7.96% and increase c-HDL= 0.5%.
8	Ruscica, M, *et al.*,[23]	2019	Italy	N=32 patients Group 1: Nutraceutical combination (probiotic *Bifidobacterium longum* BB536 and RYR extract), group 2: placebo.	12 weeks	Group 1: Reduced TC (16.7%) and c-LDL (25.7%)
9	Ahmadian, Fatemeh, *et al.*,[24]	2018	Iran	N=60 patients (2 groups). Group 1 with placebo, group 2 intervention with probiotics (*Lactobacillus plantarum*, *L.acidophilus*, L.fermentum, *L. gasseri*)	6 weeks	Increase in c-HDL levels (P = 0.002) in the probiotic group. In addition to the decrease in the atherogenic index (1.09)
10	Costabile, Adele, *et al.,* [25]	2017	United Kingdom	N=46 humans, 2 groups Group 1: placebo Group 2: intervention with *Lactobacillus plantarum* ECGC 13110402 ($2x10^9$ CFU)	12 weeks	Group 2: TC=36.7% reduction, c-HDL= increased 0.23 mmol/l, c-LDL = decreased 0.39 mmol/l (13.9%).
11	Fuentes, *et al.*,[26]	2016	Spain	N=60 patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactobacillus plantarum* (LpPRO)	12 weeks	In the group with probiotic intervention, there was a 24.4 mg/dL reduction in c-LDL, a decrease in total cholesterol (33.7 mg/dL), an increase in c-HDL (2.9 mg/dL), and a decrease in of serum TG levels (29.1 mg/dL)
12	Kullisaar Tiiu, *et al.*,[27]	2016	Estonia	N= 45 patients. Group 1: consume Reg'Activ Cholesterol capsules, group 2 receive a placebo. Who consumed RAC containing an antioxidant and antiatherogenic probiotic *Lactobacillus fermentum* ME-3 (LFME-3)	4 weeks	With the intervention of the probiotic, the levels of TC (12.3%), c-LDL (17.7%) and TG (4.37) were reduced, and c-HDL (4.37%) increased.
13	Rajkumar H, *et al.*,[28]	2014	India	N= 60 overweight adults (4 groups). Group 1 with placebo, group 2 treatment with probiotic VSL#3 (*Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium* breve, *Lactobacillus acidophilus*, *Lactobacillus paracasei, Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus plantarum, Streptococcus salivarius subsp. thermophilus*), group 3 supplemented with Omega 3, group 4 probiotic plus Omega 3.	6 weeks	In group 4 (probiotics plus Omega 3) c-HDL increased by 21.06%, c-LDL, triglycerides and TC decreased by 10.45%, 7.5%, 4.94%, respectively. Being this group where the lipid profile was improved the most.

14	Nabavi S, *et al.*,[29]	2014	Iran	N=72 patients diagnosed with nonalcoholic fatty liver disease (NAFLD) in 2 groups. Group 1: conventional yogurt and group 2: probiotic yogurt (*Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12)	8 weeks	In group 2 TC reduced 4.1% and c-LDL 6.92% compared to group 1.
15	Fuentes, *et al.*,[30]	2013	Spain	N=60 hypercholesterolaemic patients (2 groups). Group 1 with placebo, group 2 intervention with *Lactobacillus plantarum* strains CECT 7527, CECT 7528 and CECT 7529	12 weeks	Treatment with the three strains of *L. plantarum* showed a reduction in TC levels (17.4%), and c-LDL (17.6%).
Articles on rats						
16	Zafar Hamza, *et al.*,[31]	2022	Pakistan	N=55 rats, 11 groups. Group 1: Diet 1. High-Fat Diet (HCFD), Group 2: High-Fat Diet and with Statin Treatment (SDHF), Group 3: Normal Diet, Groups 4-11: HCFD Diet plus probiotics such as: *Lacticaseibacillus rhamnosus* FM9, *Limosilactobacillus fermentum Y57*, etc.	30 days	Group 2: Decreased total cholesterol level (5%) and c-HDL improved 46%. Groups 4 to 11: Decrease in cholesterol, especially *L. rhamnosus* FM9 (9%), *L. fermentum* Y57 (8%) and *L. fermentum* FM6 (7%), decrease in c-LDL with strains Y57 (41%), FM9 (37%) and FM6 (31%).
17	Munir, *et al.*, [32]	2022	Pakistan	N=30 rats, 5 groups: Group 1: negative control, group 2: positive control, group 3: HFCD plus *L. brevis* MT950194, group 4: HFCD plus *L. brevis* MW365351, group 5: HFCD plus a mixture of the two investigated probiotics.	75 days	The reduction of TC in groups 3 and 4 was 54%, while in group 5 it was 60%, which indicates a better lipid-lowering action when the two strains are combined.
18	Fossi, *et al.*, [33]	2022	Cameroon	N= 18 rats, 3 groups: Group 1: feeding with HFCD plus pw4 (*L. plantarum*), group 2: negative control (oral gavage with deionized water), group 3: HFCD plus deionized water.	4 weeks	In group 1, the levels of TC (17.2%), TG (32.14%), and c-LDL (69.5%) were significantly reduced, the level of HDL-C (75.8%) increased, compared to group 3.
19	Abdelshafy, A. M., *et al.,* [34]	2022	Egypt	N=40 rats. Group 1 (control): Basal diet, group 2: Basal diet with non-fermented quinoa, Group 3: Diet with quinoa fermented by *L. plantarum,* Group 4: Diet with quinoa fermented by *L. delbrueckii subsp. bulgaricus*.	30 days	Group 3: reduction of TC (6.48%), c-LDL (43.64%) and TG (18.76%). Increase in c-HDL levels (25.08%). Group 4: reduction of TC (4.58%), c-LDL (39.46%) and TG (12.46%). Increase in HDL-C (19.35%).

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20	Asad F., *et al.,*[35]	2020	Pakistan	N=40 hypercholesterolemic rats. Group 1: Hypercholesterolemic diet (HC-CON), group 2: HC diet and supplemented with *Agaricus bisporus* mushrooms (HC-*A. bisporus*), group 3: mixture of probiotic (Protexin; Probiotics International Ltd., Somerset, UK) (HC-PB) and group 4: combination of AB and mixture of probiotics (HC-AB.PB).	6 weeks	Group 3: c-HDL levels increased (1.98%). The values of TC (19.41%), c-LDL (5.96%), and TG (34.10%) decreased. Group 4: c-HDL levels increased (7.62%). The values of TC (11.24%), c-LDL (13.92%), and TG (30.25%) decreased.
21	Wa Y, *et al.,* [36]	2019	China	N=40 rats. Group 1: control (C), group 2: high fat diet (HF) model, group 3: fermented milk diet with a single probiotic (*L. rhamnosus* LV108) (HFPB) and group 4: diet with a combination fermented milk with probiotic (*L. rhamnosus* LV108-fermented milk, *L. casei* grx12-fermented milk and *L. fermentum* grup grx08-fermented milk) (HFPBS).	4 weeks	Group 3: the lipid profile reduced the TC (27.83%), the c-LDL (57.14%), and the TG (21.53%), in addition, the value of c-HDL increased (4, 0%) Group 4: reduced TC (22.71%), decreased c-LDL (35.71%) and there was also a decrease in TG (16.92%). c-HDL levels increased (2.0%) compared to group 2.
22	Nocianitri, K.A., *et al.,*[37]	2017	Indonesia	N=24 rats. Group 1: High-fat diet (HF), group 2: HF and *L. rhamnosus* SKG34 (HF-SKG34), group 3: *L. rhamnosus* FBB42 (HF-FBB42) and HF and group 4: combination of the two probiotics (*L. rhamnosus* and *L. rhamnosus* SKG34 FBB42; HF-SKG34-FBB42).	4 weeks	Compared with group 1, group 2 (HF-SKG34) reduced the levels of TC (13.60%) and c-LDL (71.22%), in addition, there was an increase in c-HDL (15.29%). Group 3 (HF-FBB42) reduced the concentrations of TC (16.22%), c-LDL (66.01%), and GT (20.76%). The levels rose c-LDL (8.71%). Group 4: decrease in TC values (13.32%), c-LDL (72.18%), and TG (17%). The amount of HDL-C increased by 15.23%.
23	Chuan, Li, *et al.*,[38]	2014	China	N= 40 rats, 4 treatment groups: Group 1: normal diet. Group 2: HFCD fed, Group 3: HFCD + *Lactobacillus plantarum* NCU116L (10^8 CFU/ml), Group 4: HFCD + *Lactobacillus plantarum* NCU116H (10^9 CFU/ml).	5 weeks	The results suggest that *L. plantarum* NCU116 was able to modify lipid metabolism and reduce cholesterol level, in particular, in HFCD rats through regulation of gene expression of key factors related to LDL receptor and CYP7A1.

24	Park Do-Young, *et al.*,[39]	2013	Republic of Korea	N=27 rats, 3 groups. Group 1: High-Fat Diet (HDF) + placebo, group 2: Normal diet, group 3: HDF + probiotic (*Lactobacillus curvatus*HY7601 y*Lactobacillus plantarum*KY1032)	10 weeks	Group 3: Total cholesterol decreased (17%) compared to group 1.
25	Salaj, *et al.*,[40]	2013	Slovakia	N= 40 rats, 4 groups: Group 1: control, group 2: HFCD, group 3: HFCD plus *Lactobacillus plantarum* LS/07, group 4: HFCD plus supplementation with *Lactobacillus plantarum* Biocenol LP96	10 weeks	The administration of *Lactobacillus plantarum* LS/07 resulted in greater decreases in TC (20%) and c-LDL (24%), while TG and VLDL levels were reduced by 39% in the group with *Lactobacillus plantarum* Biocenol LP96
26	Mohania, Dheeraj, *et al.*,[41]	2013	India	N=21 Rats on a hypercholesterolemic diet. 3 groups. Group 1 with Dahi probiotic (*Lactobacillus plantarum* Lp9), group 2: Dahi probiotic in milk, group 3: buffalo milk)	120 days	Group 1: reduction in total cholesterol (35%) and triglycerides (72%), increase in c-HDL (116%), and decrease in LDL-VLDL (59%). Group 2 and 3: increased total cholesterol and triglycerides.
27	Yoo SR, *et al.*,[42]	2013	Republic of Korea	N=50 rats, 5 groups Group 1: (HFCD), Group 2: HFCD + *L. plantarum* (*PL*) KY1032 (PL, 10^{10}CFU/día). Group 3: HFCD + *L. curvatus* (*LC*) HY7601 (CU, 10^{10}CFU/día), Group 4: HFCD + (PL y CL), Group 5: Normal diet.	9 weeks	Group 2, 3 and 4: They reduced the accumulation of fat and total cholesterol in plasma. Group 4: Decreased enzymatic activities related to the oxidation of fatty acids and their gene expressions.
28	Kumar Manoj, *et al.*, [43]	2013	India	N=35 rats, divided into 5 treatment groups. Group 1: Normal Control Diet, Group 2: Hypercholesterolemic (HD) Diet, Group 3: HD Diet + *Lactobacillus rhamnosus* GG (LGG), Group 4: HD Diet + Aloe Vera Gel, and Group 5: HD Diet + LGG Probiotic + Aloe Vera Gel.	45 days	Group 3: decrease in total cholesterol (32%) and triglycerides (41%), group 4: reduction in total cholesterol (43%), and triglycerides (23%), and group 5: decrease in triglycerides (45%) and atherogenic index at 2.45. VLDL (45%) and c-LDL (30%).
29	Huang, Ying, *et al.*,[44]	2013	China	N= 40 rats, 3 treatment groups: Group 1: High cholesterol diet (HC), Group 2: HC diet + *Lactobacillus plantarum* Lp09 (HC-Lp09) and Group 3: HC diet + *Lactobacillus plantarum* Lp45 (HC-Lp45).	4 weeks	Group 2: reduced TC= 30.5%, TG= decrease 23.7%, c-LDL: 47.9% reduction Group 3: reduced TC =18.4%, TG= 12.3% reduction, c-LDL = 21.5% reduction

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30	Park Do-Young, *et al.*,[45]	2013	South Korea	N=36 rats. Group 1: Probiotic with low dose LP (*L. plantarum* and *L. curvatus* 10^9 CFU), Group 2: Probiotic with high dose HP *(L. plantarum* and *L. curvatus* – 10^{10} UFC) and Group 3: With placebo (High fructose diet: HF)	6 weeks	Treatment with high or low dose probiotics helped lower triglycerides by 46% compared to group 3.

TC, total cholesterol; TCp postprandial total cholesterol; TG, triglycerides; c-LDL; pc-LDL, postprandial low density cholesterol; c-HDL: high density cholesterol; N, sample; HFCD, High-Fat Diet; CFU, Colony Forming Units.

The selected bibliography indicates that the investigations of probiotic supplementation have beneficial effects in the reduction of hyperlipidemia, decreasing the level of total cholesterol by 16,65%, the decrease in the concentration of c-LDL by 32,02%. In addition, an increase of 21,71% of the c-HDL level was demonstrated in the study subjects, with respect to the concentrations of triglycerides, a 29,67% decrease is reported in some articles. The trials using probiotics were carried out from 3 to 12 weeks, concluding the minimum period of consumption in which probiotics manifest their benefits which is after 6 weeks. The probiotics that were used are *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lacticaseibacillus rhamnosus*, *Limosilactobacillus fermentum*, *Lactobacillus curvatus*, *Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus crispatus, Lactobacillus casei, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus, Streptococcus salivarius subsp. thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium infantis, Bacillus subtilis* and *Lactobacillus gasseri.*

Study characteristics

The date range of the articles was from 2013 to 2023. The investigations were carried out: two from Indonesia, one from Brazil, two from Italy, four from China, three from Spain, one from EE.UU., three from Iran, one from Egypt, one from the United Kingdom, one from Estonia, three from India, three from Pakistan, one from Cameroon, two from the Republic of Korea, one from Slovakia and one from South Korea.[16-45]

Population studied

The tested population consisted of fifteen human investigations, between women and men, (total N=1099, n=102 children and n=997 adults)16-30 and in fifteen investigations they included rats (total N=536).[31-45]

Instruments used to measure

The database software used in the articles selected for the systematic review were MINITAB for Windows 11.[21] and nine were registered in SPSS (Statistical Package for Social Sciences). Subsequently, the statistical tests for comparison between the groups in each particular s7tudy were: Tukey's test, Duncan's method, ANOVA, Friedman, MANCOVA, Chi-square, similarity analysis (ANOSIM), unpaired and unpaired Student's T test, U Mann-Whitney and Newman-Keuls multiple comparisons test. In addition, the Kolmogorov–Smirnov test was used for the distribution of data in one article, and the Bonferroni post-hoc test was used to determine the simultaneous confidence level for a set of intervals.[16-45]

Record appraisal

The objectives set out in the investigations were clear, they had study designs in accordance with the purposes they sought. Fifteen investigations involved humans,[16-30] and 15 rats.[31-45] The variables were considered and measured according to each investigation correctly, as well as the risk factors considered with respect to the stated objectives.[16-45] The effects of the probiotics in the reduction of the lipid profile were evaluated with conventional methods and in the period between 30 days and 12 weeks.[16-45] The following table 2 and 3 presents the summary of the variables of the selected articles.

TABLE 2. Record appraisal

	Authors	Aims/ Clear objectives	Study design appropriate for the stated aim(s)	Sample size justified	Target population defined	Sample appropriate to represent the target population	Selection process of participants likely to represent the target population	Measures undertaken to address non responders	Risk factors and outcome variable measure appropriately to the aims	Clear statistical significance defined
1	Karyana I.P.G., *et al.,* (2022)	YES	YES	YES	YES	NO	YES	NO	YES	YES
2	Fortes PM, *et al.,* (2020)	YES	YES	YES	YES	NO	YES	NO	YES	YES
3	Guardamagna, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
4	AkbariRad M, *et al.,* (2023)	YES	YES	YES	YES	NO	YES	NO	YES	YES
5	Wang S, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
6	Guerrero-Bonmatty R, *et al.*, (2021)	YES	YES	YES	YES	YES	YES	NO	YES	YES
7	Trotter RE, *et al.*, (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES
8	Ruscica, M, *et al.*, (2019)	YES	YES	YES	YES	YES	YES	NO	YES	YES
9	Ahmadian, Fatemeh, *et al.*,(2018)	YES	YES	YES	YES	YES	YES	NO	YES	YES
10	Costabile, Adele, *et al.*, (2017)	YES	YES	YES	YES	YES	YES	NO	YES	YES
11	Fuentes, *et al.*, (2016)	YES	YES	YES	YES	YES	YES	NO	YES	YES
12	Kullisaar Tiiu, *et al.*, (2016)	YES	YES	YES	YES	YES	YES	NO	YES	YES
13	Rajkumar H, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
14	Nabavi S, *et al.*, (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
15	Fuentes, *et al.*, (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
16	Zafar Hamza, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
17	Munir, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
18	Fossi, *et al.*, (2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES

https://doi.org/10.36105/psrua.2023v3n6.02

19	Abdelshafy, A. M., *et al.,*(2022)	YES	YES	YES	YES	YES	YES	NO	YES	YES
20	Asad F., *et al.,* (2020)	YES	YES	YES	YES	YES	YES	NO	YES	YES
21	Wa Y, *et al.,* (2019)	YES	YES	YES	YES	YES	YES	NO	YES	YES
22	Nocianitri, K.A., *et al.,* (2017)	YES	YES	YES	YES	YES	YES	NO	YES	YES
23	Chuan, *et al*., (2014)	YES	YES	YES	YES	YES	YES	NO	YES	YES
24	Park Do-Young, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
25	Salaj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
26	Mohania, Dheeraj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
27	Yoo SR, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
28	Kumar Manoj, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
29	Huang, Ying, *et al*., (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES
30	Park Do-Young, *et al.,* (2013)	YES	YES	YES	YES	YES	YES	NO	YES	YES

TABLE 3. Continuation of record appraisal

	Methods described sufficiently to be repeated	**Basic data described**	**Response rate described**	**Ifappropriate, information about non responders described**	**Results internally consistent**	**Presence of results for the analyses described**	**Discussion and conclusions justified**	**Limitationsdiscussed**	**Fundingor conflict of interests that could affect results**	**Ethical approval or informed consent attained**
1	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
2	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
3	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
4	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES

5	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
6	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
7	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES
8	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
9	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
10	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
11	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
12	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
13	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
14	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
15	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
16	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
17	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES
18	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
19	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
20	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
21	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
22	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
23	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
24	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
25	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES
26	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES
27	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
28	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES

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29	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES
30	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES

DISCUSSION

Various investigations indicate that the intestinal microbiota can intervene in multiple mechanisms such as, the production of specific substances peptides, vitamins, fatty acids, etc., help the intestinal barrier, influence the endocrine, nervous, immune systems and metabolism lipids, among other functions.[46,47] Cardiovascular diseases are increasing, and conventional treatments to treat them include drugs and diet, but there is currently evidence that some probiotic strains can improve the lipid profile and hypercholesterolemia. The use of probiotic supplements is a topic that has currently gained more interest in the general population, due to the search for new therapies and treatments for various pathologies.

Cholesterol reduction from probiotics happens through some mechanisms such as interference of cholesterol bioavailability in the small intestine, producing short-chain fatty acids through colonic fermentation of indigestible carbohydrates, and deconjugating bile salt hydrolase production. Bile acids, which is the best-known mechanism for performing the lipid-lowering effect.[10] Among the scientific community, multiple investigations have also been carried out to find out more benefits of probiotic bacteria to help in the problem of hyperlipidemia that can cause more severe problems such as, cardiovascular events, Hendijani F, *et al*. (2018), conducted a systematic review and meta-analysis of 641 randomized controlled trials where they conclude that for the control of dyslipidemia and hypertension in type 2 diabetic patients the use of probiotics reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP), TC, c-LDL, c-HDL and TG.[48] This same effect was evaluated in a meta-analysis of 14 randomized placebo-controlled trials in 702 participants demonstrating that probiotics in fermented milk generate a reduction of 3,10 mmHg (95% CI: 24,64; 21,56) in systolic BP and 1,09 mmHg (95% CI 22,11; 20,06) in diastolic BP in prehypertensive and hypertensive subjects.[49] Some research that talks about the benefits of probiotics in relation to the effect on lipid metabolism is the case of a meta-analysis of 32 controlled trials with 1971 patients that concludes that probiotic supplements can produce a reduction in total cholesterol. It is recognized that a longer consumption use in the form of capsules can increase the curative effect.[50]

In the present review, it was found that various probiotics such as *Lactobacillus plantarum, L. acidophilus, L. fermentum, L. gasseri, L. curvatus, L. rhamnosus*, among others can help reduce TC and c-LDL levels, in turn raise the level of c-HDL. This also, in accordance with what was mentioned by the research of Hu YM, et al., that probiotics are a biotherapeutic potential that improve lipid metabolism.[51] Or in the case of the findings of Sharma S, *et al.* (2016), it is concluded that the serum levels of total cholesterol and c-LDL are significantly reduced, which helps in the risk of cardiovascular diseases.[52]

This review found that the consumption of probiotic supplements helps reduce total cholesterol by 16.65% and c-LDL by 32.02%. In addition, they raise the concentration of c-HDL by 21,71%, and reduce the concentration of TG (29,67%), this agrees with Shimizu M, *et al*., (2015), in the meta-analysis of 11 randomized clinical trials in patients with normal hypercholesterolemia or mild, probiotic supplementation which demonstrate reduction in total cholesterol (TC) (mean difference -0,17 mmol/L, 95% CI -0,27 to -0,07 mmol/L) and c-LDL. (Mean difference -0,22 mmol/L, 95% CI -0,30 to -0,13 mmol/L).[53]

Strengths

This systematic review is so far the only one that focuses specifically on the percentage of modification exerted by probiotics on the lipid profile. In addition, it is a current investigation, which contemplates some variables such as the reduction of total cholesterol, c-LDL and the increase in c-HDL, which is important for cardiovascular health.

Limitations

We found some limitations in this research, some articles are not freely available, others do not mention the results

clearly or with the values expressed as a percentage, in the case of the effect of probiotics on the level of triglycerides, very few researchers mention the result. Different investigations were outside the searched time period.

CONCLUSIONS

Supplementation with specific strains of probiotics has a lipid-lowering effect, it especially reduces hypercholesterolemia through various mechanisms, but more studies are required to determine the dosage and treatment time. This review reveals that a larger number of experiments in humans and with supplementation over a longer time range are needed to verify the effects of probiotics specifically in relation to lipid profile.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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