META-ANALYSIS

Potential Value of Probiotics on Lipid Profiles in Hyperlipidemia and Healthy Participants: Systematic Review and Meta-Analysis

Dongdong Su, MD; Yan Liu, MD; Li Zhang, PhD; Shanshan Zhao, PhD; Yifei Wang, MD; Rutao Bian, PhD; Bianling Xu, PhD; Xiaoyang Chen, PhD; Xuegong Xu, PhD

ABSTRACT

Objective • Many randomized controlled trials (RCTs) have reported the effect of probiotics on reducing plasma lipids with inconsistent results. An explicit systematic review and meta-analysis were conducted in this study to evaluate the effect of probiotics on the lipid profile of healthy and hyperlipidemia participants.

Methods • A comprehensive literature search of RCTs was conducted using PubMed, Embase, World Health Organization (WHO) Global Index Medicus, WHO clinical trial registry, and Clinicaltrials.gov. Inclusion criteria included RCTs comparing the use of any strain of a specified probiotic with the placebo control group. The change in lipid profiles was analyzed.

Results • The probiotics can decrease the total cholesterol (TC) level in hyperlipidemia participants but not healthy persons (MD = -0.43, 95% CI -0.60 – -0.25, $P < .01$; MD = -0.09, 95% CI -0.26 – 0.08, $P > .05$). Probiotics did not reduce high-density lipoprotein cholesterol (HDL-C) in patients with hyperlipidemia or healthy people (MD = -0.01, 95% CI -0.09 – 0.07, $P > .05$; MD = 0.02, 95% CI -0.04 – 0.09, $P > .05$). Furthermore, probiotics can reduce the low-density lipoprotein cholesterol (LDL-C) level both in hyperlipidemia and healthy persons (MD = -0.34, 95% CI -0.43 – -0.26, $P < .01$; MD = -0.15, 95% CI -0.28 – -0.02, $P < .05$). Lastly, the effect of probiotics on reducing triglyceride (TG) levels was significant in hyperlipidemia persons but not in the healthy population (MD = -0.20, 95% CI -0.37 – -0.04, $P < .01$; MD = -0.01, 95% CI -0.02 – 0.04, $P > .05$).

Conclusions • Through our analysis, the effect of probiotics on lowering plasma lipid was more obvious in hyperlipidemia participants than healthy population. However, further studies are required to confirm the findings due to pronounced clinical heterogeneity. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Hyperlipidemia refers to an imbalance of cholesterol in the blood, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). They regulate cholesterol levels in the blood, and cholesterol imbalances may increase the risk of cardiovascular and cerebrovascular diseases, including myocardial infarction and stroke. Other forms of hyperlipidemia include hypertriglyceridemia as well as mixed hyperlipidemia, in which both cholesterol and triglyceride (TG) levels are elevated.[1] The development of hyperlipidemia is related to many factors, such as high-fat diet, smoking, chronic kidney disease, diabetes, hypertension, and genetic factors.[2] Taking targeted preventive measures against these risk factors is the key to preventing hyperlipidemia and secondary cardiovascular events.

Animal experiments suggest that intestinal flora plays an important role in regulating lipid metabolism in the host. The disturbance of lipid metabolism could induce changes in the intestinal environment, which could induce dysbiosis of internal microflora. Normal gut microbiota is essential in maintaining lipid-metabolism homeostasis, including mediating satiety in

the brain through microglia and vagus nerves, regulating cholesterol metabolism in the liver, promoting lipid oxidation in the muscle and energy storage in the adipose tissue, and maintaining the integrity of the intestinal barrier.[3-5] Some related interventions, such as fecal microbiological transplantation and probiotics, have achieved good results in the treatment of hyperlipidemia.[6] Probiotics are active microorganisms that are beneficial to the host by regulating the immune function of the host mucosa and the system, and by regulating the balance of intestinal flora.[6,7] It has been revealed that several probiotic strains are able to improve at least one lipid fraction in both animal and human models.[8]

Many randomized controlled trials (RCTs) have reported the effect of probiotics on reducing plasma cholesterol levels with inconsistent results,[9-26] most likely due to variations in experiment design and methodological measurements. Some recent studies have been published to demonstrate the benefits of probiotics. However, they did not compare the cholesterol-lowering effects of probiotics in healthy individuals and those with hyperlipidemia,[27] and just considered the effect of probiotics on total cholesterol.[28] Therefore, an explicit systematic review and meta-analysis are needed to evaluate the effect of probiotics on reducing plasma cholesterol levels in healthy and hyperlipidemia participants.

MATERIALS AND METHODS

Study Selection

All RCTs evaluating the effect of probiotics on lipid profiles in healthy and hyperlipidemia persons were searched using PubMed (1966-2022), Embase (1980-2022), and World Health Organization (WHO) Global Index Medicus. Unpublished or ongoing studies were identified by checking clinical trial registers through Clinicaltrials.gov and WHO clinical trial registry. Literature in all languages was included in the search. Meta-analyses and systematic reviews were also hand-searched to find relevant literature that might have been missed by the initial search. Logical combinations of "probiotics" and "hyperlipidemia" were used as keywords to search for relevant literature. RCTs of any kind of probiotics and dose were accepted, either in healthy persons or hyperlipidemia patients, who did not have underlying diseases such as cardiovascular disease, kidney disease, and diabetes. Pregnant women were excluded from the study. Control groups were those that did not receive any probiotics.

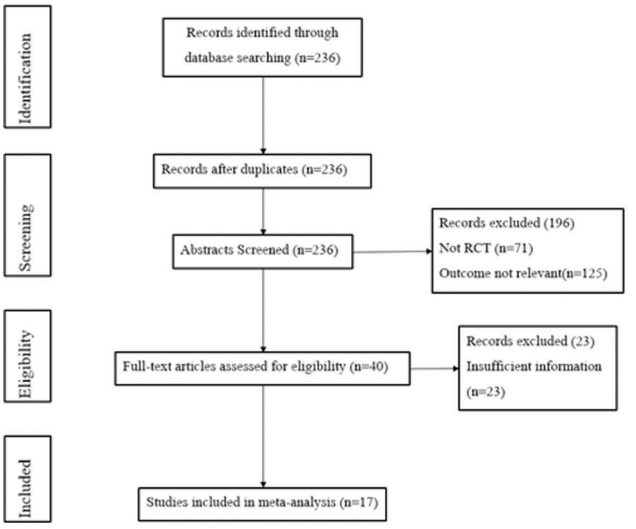
Data Extraction

Articles retrieved from the searches were evaluated independently by 2 reviewers (Bianling Xu and Shanshan Zhao) using predefined standardized data extraction forms, and then data were evaluated by a third reviewer (Li Zhang) independently based on the US National Institute of Health National Heart, Lung, and Blood Institute (NHLBI) study quality assessment tool for controlled intervention studies.[29] Clinical outcome of interest was the changes in lipid profiles after administration of probiotics compared to the control. Data pertaining to the participants, the kinds of probiotics used, control groups, and methodology were extracted (Table 1).

Table 1. Characteristics of All Randomized Control Trials Evaluating the Use of Probiotics on Lipid Profiles in Healthy and Hyperlipidemia Participants (1966–2022)

Study name	Participants	Probiotics	No. of participants (Male/Female)		Follow-up period (weeks)
			Intervention	Control	
Agerbaek 1995	Healthy	*S. thermophilus, E. faecium*	29/0	28/0	6
Ataie 2009	Hyperlipidemia	*L. acidophilus, B. lactis*	4/10	4/10	6
Bertolami 1999	Hyperlipidemia	*E. faecium, S. thermophilus*	11/21	11/21	8
Greany 2008	Healthy	*L. acidophilus, B. longum*	15/22	7/11	8
Simons 2006	Hyperlipidemia	*L. fermentum*	8/15	8/13	10
Sadrzadeh 2010	Healthy	*L. bulgaricus, L. acidophilus, S. thermophilius, B. lactis*	0/30	0/30	6
Jones 2012	Hyperlipidemia	*L. reuteri*	28/39	27/34	9
Anderson 1999	Hyperlipidemia	*L. acidophilus*	9/12	9/10	4
Fabian 2006	Healthy	*S. thermophilus, L. bulgaricus, L. casei*	0/17	0/16	4
Fuentes 2013	Hyperlipidemia	*L. plantarum*	30	30	12
Xiao 2003	Healthy	*B. longum*	16/0	16/0	4
Valentini 2015	Healthy	VSL#3	31	31	8
Rerksuppaphol 2015	Hyperlipidemia	*L. acidophilus, B. bifidum*	12/19	10/23	6
Cavallini 2016	Hyperlipidemia	*E. faecium, L. helveticus*	17/0	15/0	6
Chiu 2021	Hyperlipidemia	*L. acidophilus, L. casei, B. lactis*	20	20	12
Guerrero 2021	Hyperlipidemia	*L. plantarum*	18	18	12
Lee 2017	Healthy	*B. animalis, B. lactis*	26	25	4

Figure 1. PRISMA Flow Diagram Showing the Process of Literature Screening, Study Selection, and Reasons for Exclusion



Meta Analysis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement methodology[30] was adhered to. The mean difference (MD) with a 95% CI for lipid profiles of each trial was calculated to estimate treatment effects. Meta-analysis of the pooled data was performed using the fixed-effect model or random-effect model, depending upon the heterogeneity of the included studies. If clinical heterogeneity was observed, data was analyzed using a random-effect model. Heterogeneity was quantified using the Cochrane's Q statistic and statistics, with the values of 25%, 50%, and 75% signifying the limits of low, moderate, and high statistical heterogeneity, respectively.[31] A funnel plot was used to explore publication bias for the studies.[32] A two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed using the R package *meta* (R version 4.0.1). The risk of bias was evaluated using the

Cochrane risk of bias tool. It was used to evaluate the selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

RESULTS

Demographic Characteristics of the Studies

The literature search process, shown in Figure 1, identified 236 potential studies for full analyses. Following the application of exclusion criteria, 17 studies were identified as appropriate for further quantitative meta-analyses (Table 1). Of 17 studies included in the final analysis, 7 studies included healthy participants, while 10 studies were conducted in hyperlipidemia patients. The probiotic strains used were *L. acidophillus, L. casei, L. paracasei, L. bulgaricus, L. fermentum, L. helveticus, L. paracasei, L. plantarum, L. reuteri, B. bifidum, B. lactis, B. longus, B. longum, S. thermophilus, E. faecium*. The follow-up period ranged from 4 weeks to 12 weeks. The present study compared lipid changes at the end of follow-up between the intervention and treatment groups.

Effects of probiotics on total cholesterol (TC) in healthy and hyperlipidemia participants

Overall, probiotics can lower the level of TC as compared to the control group who did not receive probiotics (MD = -0.28, 95 % CI -0.43 – -0.13, $P < .01$; Figure 2). There was significantly high heterogeneity between the trials ($I^2 = 86\%$). Of 17 studies included in the final analysis, 7 studies involved healthy participants, while 10 studies were conducted in hyperlipidemia patients. In the healthy subgroup, no significant difference was observed in the level of TC compared to the control group (MD = -0.09, 95% CI -0.26 – 0.08, $P > .05$; Figure 2). High heterogeneity was observed between the studies ($I^2 = 82\%$). In the hyperlipidemia subgroup, the meta-analysis showed a significantly lower level of TC compared to the control group (MD = -0.43, 95% CI -0.60 – -0.25, $P < .01$; Figure 2). There is moderate heterogeneity between the studies ($I^2 = 69\%$). The subgroup difference between healthy and hyperlipidemia participants was significant ($P < .01$).

Effects of probiotics on HDL-C in healthy and hyperlipidemia participants

Overall, probiotics cannot lower the level of HDL-C as compared to the control group who did not receive probiotics (MD = 0.00, 95 %CI -0.05 – 0.05, $P > .05$; Figure 3). There was high heterogeneity between the trials ($I^2 = 88\%$). Of 15 studies included in the final analysis, 6 studies involved healthy participants, while 9 studies were conducted in hyperlipidemia patients. In the healthy subgroup, the level of HDL-C showed no significant difference compared to the control group (MD = 0.02, 95% CI -0.04 – 0.09, $P > .05$; Figure 3). Moderate heterogeneity was observed between the studies ($I^2 = 71\%$). In the hyperlipidemia subgroup, the meta-analysis showed no significant difference in the HDL level compared to the control group (MD = -0.01, 95% CI -0.09 – 0.07, $P > .05$; Figure 3). There is high heterogeneity between the studies ($I^2 = 92\%$). The subgroup difference between healthy and hyperlipidemia participants was not significant ($P = .51$).

Figure 2. Forest Plot of Probiotics from Randomized Controlled Trials Demonstrating the Effect on the Mean Difference of Total Cholesterol in Healthy and Hyperlipidemia Participants

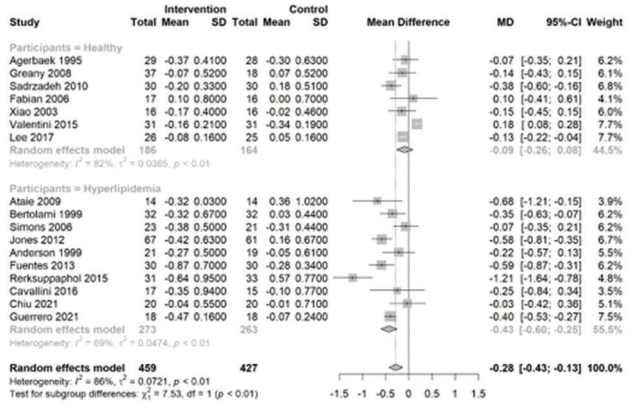


Figure 3. Forest Plot of Probiotics from Randomized Controlled Trials Demonstrating the Effect on the Mean Difference of High-Density Lipoprotein in Healthy and Hyperlipidemia Participants

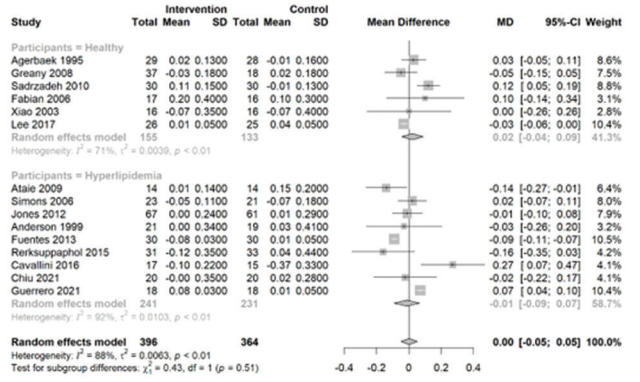


Figure 4. Forest Plot of Probiotics from Randomized Controlled Trials Demonstrating the Effect on the Mean Difference of Low-Density Lipoprotein in Healthy and Hyperlipidemia Participants

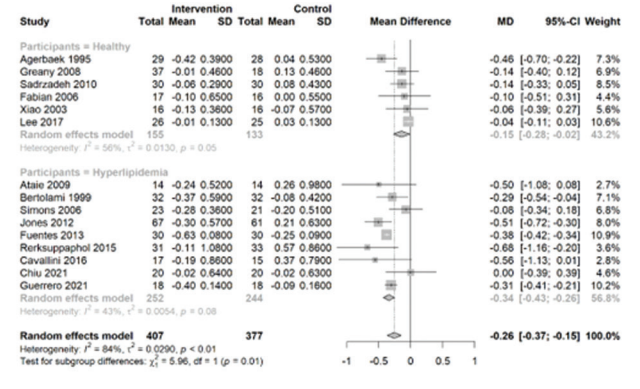


Figure 5. Forest Plot of Probiotics from Randomized Controlled Trials Demonstrating the Effect on the Mean Difference of Triglyceride in Healthy and Hyperlipidemia Participants

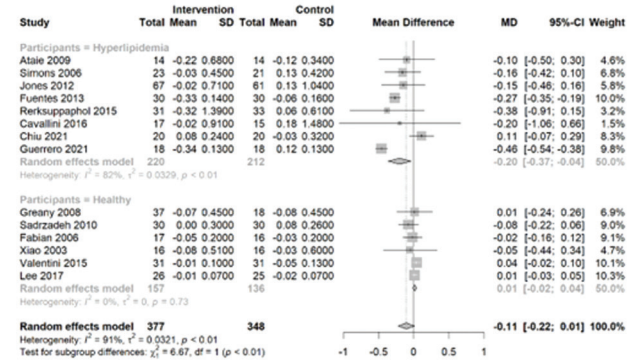


Figure 6. Funnel Plots of Included Randomized Controlled Trials Demonstrating the Treatment Effect Relative to Study Size in (A) Total Cholesterol, (B) High-Density Lipoprotein, (C) Low-Density Lipoprotein, and (D) Triglyceride Solid black dots represent the true effect values.

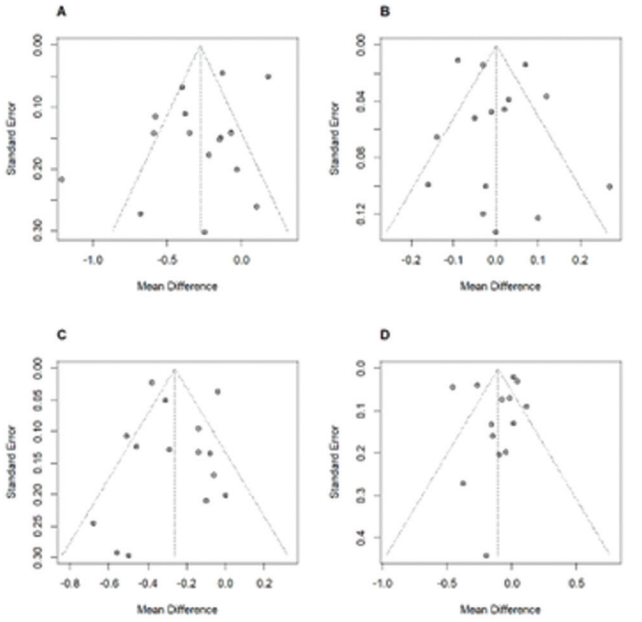
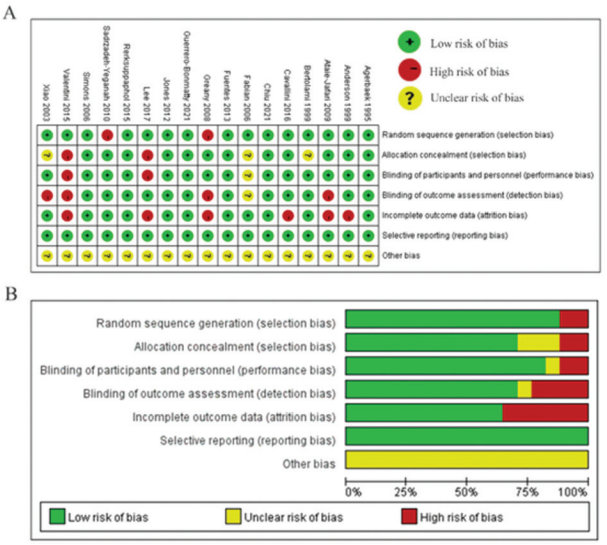


Figure 7. Risk of Bias Analysis for the Studies Included



Effects of probiotics on LDL in healthy and hyperlipidemia participants

Overall, the probiotics can lower the level of LDL-C as compared to the control group who did not receive probiotics (MD = -0.26, 95% CI -0.37 – -0.15, P < .05; Figure 4). There was high heterogeneity between the trials (I^2 = 84%). Of 15 studies included in the final analysis, 6 studies involved healthy participants, while 9 studies were conducted in hyperlipidemia patients. In the healthy subgroup, the level of LDL-C showed significantly lower differences compared to the control group (MD = -0.15, 95% CI -0.28 – -0.02, P < .05; Figure 4). Moderate heterogeneity was observed between the studies (I^2 = 56%). In the hyperlipidemia subgroup, the meta-analysis showed a significantly lower level of LDL-C compared to the control group (MD = -0.34, 95% CI -0.43 – -0.26, P < .01; Figure 4). There is low heterogeneity between studies (I^2 = 43%). The subgroup difference between healthy and hyperlipidemia participants was significant (P = .01).

Effects of probiotics on TG in healthy and hyperlipidemia participants

Overall, probiotics cannot lower the level of TG in hyperlipidemia participants as compared to the control group who did not receive probiotics (MD = -0.11, 95% CI -0.22 – 0.01, P > .05; Figure 5). There was high heterogeneity between the trials (I^2 = 91%). Of 14 studies included in the final analysis, 6 studies were performed involving healthy participants, while 8 studies were conducted in hyperlipidemia patients. In the healthy subgroup, no significant difference was observed in the level of TG compared to the control group (MD = -0.01, 95% CI -0.02 – 0.04, P > .05; Figure 5). No heterogeneity was observed between the studies (I^2 = 0%). In the hyperlipidemia subgroup, the meta-analysis showed a significantly lower level of TG compared to the control group (MD = -0.20, 95% CI -0.37 – -0.04, P < .01; Figure 5). There is a high heterogeneity between the studies (I^2 = 82%). The subgroup difference between healthy and hyperlipidemia participants was significant (P < .01).

Publication Bias

Funnel plots were used to visually assess for publication bias in the treatment effect of probiotics on TC, HDL-C, LDL-C, and TG in healthy and hyperlipidemia participants (Figure 6). There was minor asymmetry on the funnel plot suggesting that studies are less likely to be published if positive outcomes are demonstrated.

Risk of Bias Analysis

The risk of bias in the studies included is summarized in Figure 7. The Cochrane risk of bias tool was used to evaluate the selection bias, performance bias, detection bias, attrition bias, and other biases.

DISCUSSION

In vitro and *in vivo* experiments as well as cohort studies have shown that probiotics play an important role in lowering blood lipids by regulating intestinal flora.[33,34] In the present study, we evaluated the effect of probiotics on lipid profiles in healthy and hyperlipidemia participants explicitly and systematically.

Through our analysis, the effect of probiotics on lowering blood lipids is different in hyperlipidemia participants and healthy populations. Probiotics can decrease the TC level in hyperlipidemia participants but not healthy persons as compared to the control group who received placebo (MD = -0.43, 95% CI -0.60 – -0.25, $P < .01$; MD = -0.09, 95% CI -0.26 – 0.08, $P > .05$, respectively). The subgroup difference between them was significant. The lowering effect of probiotics on HDL-C was not detected either in hyperlipidemia participants or in healthy persons (MD = -0.01, 95% CI -0.09 – 0.07, $P > .05$; MD = 0.02, 95% CI -0.04 – 0.09, $P > .05$, respectively). It can be concluded that the probiotics can reduce the LDL-C level both in hyperlipidemia and healthy persons (MD = -0.34, 95% CI -0.43 – -0.26, $P < .01$; MD = -0.15, 95% CI -0.28 – -0.02, $P < .05$, respectively). The subgroup difference between them was significant. Therefore, the effect of probiotics on lowering LDL-C in participants with hyperlipidemia was more obvious than that in healthy population. The effect of probiotics on reducing TG level was significant in hyperlipidemia persons but not in healthy population (MD = -0.20, 95% CI -0.37 – -0.04, $P < .01$; MD = -0.01, 95% CI -0.02 – 0.04, $P > .05$, respectively).

However, although probiotic use has been greatly popularized among the general public, there are conflicting clinical results for many probiotic strains and formulations.[35] Theoretical risks have been described in case reports, clinical trial results, and experimental models, including systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, gene transfer, and gastrointestinal side effects.[36,37] The included studies did not report the incidence of side effects and mortality after administration of probiotics. Therefore, probiotics should be used in consideration of their possible side effects, which need to be confirmed by more studies.

Some limitations of this study should be acknowledged. First, the composition of probiotics used in each study varied, and different probiotic strains or antibiotics may present different values in lowering plasma lipids. Second, the duration of administration of probiotics was different in the studies included, which should be important for the outcomes and could account for the high clinical heterogeneity. Third, we did not distinguish the difference in the lowering lipid effect of probiotics in different genders. Moreover, there was an imbalance in the ratio of men to women between the treatment and control groups in the included studies. Despite these limitations, our findings support the fact that the effects of probiotics on lowering plasma lipids were more obvious in hyperlipidemia participants than in healthy populations. However, further studies are required to be conducted to confirm the findings due to pronounced clinical heterogeneity.

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AUTHOR DISCLOSURE STATEMENT

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

AUTHOR CONTRIBUTIONS

Dongdong Su and Yan Liu contributed equally to this work and should be considered co-first authors. We thank every participant who contributed to the study. The authors' responsibilities were as follows—Xuegong Xu and Xiaoyang Chen: research design; Rutao Bian, Dongdong Su, Yifei Wang, and Yan Liu: data collection; Yan Liu and Dongdong Su: data analysis; Bianling Xu, Shanshan Zhao, and Li Zhang: data assessment; Dongdong Su: Manuscript writing.

REFERENCES

1. Karr S. Epidemiology and management of hyperlipidemia. *Am J Manag Care*. 2017;23(9)(suppl):S139-S148.
2. Mozaffarian D, Benjamin EJ, Go AS, et al; Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: A report from the american heart association. *Circulation*. 2016;133(4):e38-e360. doi:10.1161/CIR.0000000000000350
3. Jia X, Xu W, Zhang L, Li X, Wang R, Wu S. Impact of Gut Microbiota and Microbiota-Related Metabolites on Hyperlipidemia. *Front Cell Infect Microbiol*. 2021;11:634780. doi:10.3389/fcimb.2021.634780
4. Fukuda S, Ohno H. Gut microbiome and metabolic diseases. *Semin Immunopathol*. 2014;36(1):103-114. doi:10.1007/s00281-013-0399-z
5. Jia X, Xu W, Zhang L, Li X, Wang R, Wu S. Impact of Gut Microbiota and Microbiota-Related Metabolites on Hyperlipidemia. *Front Cell Infect Microbiol*. 2021;11:634780. doi:10.3389/fcimb.2021.634780
6. Lai ZL, Tseng CH, Ho HJ, et al. Fecal microbiota transplantation confers beneficial metabolic effects of diet and exercise on diet-induced obese mice. *Sci Rep*. 2018;8(1):15625. doi:10.1038/s41598-018-33893-y
7. Wieërs G, Belkhir L, Enaud R, et al. How probiotics affect the microbiota. *Front Cell Infect Microbiol*. 2020;9:454. doi:10.3389/fcimb.2019.00454
8. Sharma S, Puri S, Kurpad AV. Potential of probiotics in hypercholesterolemia: A review of in vitro and in vivo findings. *Altern Ther Health Med*. 2018;24(2):36-43.
9. Agerbaek M, Gerdes LU, Richelsen B. Hypocholesterolaemic effect of a new fermented milk product in healthy middle-aged men. *Eur J Clin Nutr*. 1995;49(5):346-352.
10. Anderson JW, Gilliland SE. Effect of fermented milk (yogurt) containing Lactobacillus acidophilus L1 on serum cholesterol in hypercholesterolemic humans. *J Am Coll Nutr*. 1999;18(1):43-50. doi:10.1080/07315724.1999.10718826
11. Ataie-Jafari A, Larijani B, Alavi Majd H, Tahbaz F. Cholesterol-lowering effect of probiotic yogurt in comparison with ordinary yogurt in mildly to moderately hypercholesterolemic subjects. *Ann Nutr Metab*. 2009;54(1):22-27. doi:10.1159/000203284
12. Bertolami MC, Faludi AA, Batlouni M. Evaluation of the effects of a new fermented milk product (Gaio) on primary hypercholesterolemia. *Eur J Clin Nutr*. 1999;53(2):97-101. doi:10.1038/sj.ejcn.1600683
13. Cavallini DCU, Manzoni MSJ, Bedani R, et al. Probiotic soy product supplemented with isoflavones improves the lipid profile of moderately hypercholesterolemic men: A randomized controlled trial. *Nutrients*. 2016;8(1):52. doi:10.3390/nu8010052
14. Chiu HF, Fang CY, Shen YC, Venkatakrishnan K, Wang CK. Efficacy of probiotic milk formula on blood lipid and intestinal function in mild hypercholesterolemic volunteers: A placebo-control, randomized clinical trial. *Probiotics Antimicrob Proteins*. 2021;13(3):624-632. doi:10.1007/s12602-020-09728-6
15. de Roos NM, Schouten G, Katan MB. Yoghurt enriched with Lactobacillus acidophilus does not lower blood lipids in healthy men and women with normal to borderline high serum cholesterol levels. *Eur J Clin Nutr*. 1999;53(4):277-280. doi:10.1038/sj.ejcn.1600722
16. Fabian E, Elmadfa I. Influence of daily consumption of probiotic and conventional yoghurt on the plasma lipid profile in young healthy women. *Ann Nutr Metab*. 2006;50(4):387-393. doi:10.1159/000094304
17. Fuentes MC, Lajo T, Carrión JM, Cuñé J. Cholesterol-lowering efficacy of Lactobacillus plantarum CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. *Br J Nutr*. 2013;109(10):1866-1872. doi:10.1017/S000711451200373X
18. Greany KA, Bonorden MJL, Hamilton-Reeves JM, et al. Probiotic capsules do not lower plasma lipids in young women and men. *Eur J Clin Nutr*. 2008;62(2):232-237. doi:10.1038/sj.ejcn.1602719
19. Guerrero-Bonmatty R, Gil-Fernández G, Rodríguez-Velasco FJ, Espadaler-Mazo J. A combination of lactoplantibacillus plantarum strains CECT7527, CECT7528, and CECT7529 plus monacolin k reduces blood cholesterol: results from a randomized, Double-Blind, Placebo-Controlled study. *Nutrients*. 2021;13(4):1206. doi:10.3390/nu13041206
20. Jones ML, Martoni CJ, Prakash S. Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. *Eur J Clin Nutr*. 2012;66(11):1234-1241. doi:10.1038/ejcn.2012.126
21. Lee Y, Ba Z, Roberts RF, et al. Effects of Bifidobacterium animalis subsp. lactis BB-12® on the lipid/lipoprotein profile and short chain fatty acids in healthy young adults: a randomized controlled trial. *Nutr J*. 2017;16(1):39. doi:10.1186/s12937-017-0261-6
22. Rerksuppaphol S, Rerksuppaphol L. A Randomized Double-blind Controlled Trial of Lactobacillus acidophilus Plus Bifidobacterium bifidum versus Placebo in Patients with Hypercholesterolemia. *J Clin Diagn Res*. 2015;9(3):KC01-KC04. doi:10.7860/JCDR/2015/11867.5728
23. Sadrzadeh-Yeganeh H, Elmadfa I, Djazayery A, Jalali M, Heshmat R, Chamary M. The effects of probiotic and conventional yoghurt on lipid profile in women. *Br J Nutr*. 2010;103(12):1778-1783. doi:10.1017/S0007114509993801

24. Simons LA, Amansec SG, Conway P. Effect of Lactobacillus fermentum on serum lipids in subjects with elevated serum cholesterol. *Nutr Metab Cardiovasc Dis*. 2006;16(8):531-535. doi:10.1016/j.numecd.2005.10.009
25. Valentini L, Pinto A, Bourdel-Marchasson I, et al. Impact of personalized diet and probiotic supplementation on inflammation, nutritional parameters and intestinal microbiota - The "RISTOMED project": randomized controlled trial in healthy older people. *Clin Nutr*. 2015;34(4):593-602. doi:10.1016/j.clnu.2014.09.023
26. Xiao JZ, Kondo S, Takahashi N, et al. Effects of milk products fermented by Bifidobacterium longum on blood lipids in rats and healthy adult male volunteers. *J Dairy Sci*. 2003;86(7):2452-2461. doi:10.3168/jds.S0022-0302(03)73839-9
27. Sharma S, Kurpad AV, Puri S. Potential of probiotics in hypercholesterolemia: A meta-analysis. *Indian J Public Health*. 2016;60(4):280-286. doi:10.4103/0019-557X.195859
28. Wang L, Guo MJ, Gao Q, et al. The effects of probiotics on total cholesterol: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018;97(5):e9679. doi:10.1097/MD.0000000000009679
29. Study quality assessment tools | NHLBI, NIH. 2021: 2013.
30. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34. doi:10.1016/j.jclinepi.2009.06.006
31. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186
32. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
33. Yadav R, Khan SH, Mada SB, Meena S, Kapila R, Kapila S. Consumption of probiotic lactobacillus fermentum MTCC: 5898-Fermented milk attenuates dyslipidemia, oxidative stress, and inflammation in male rats fed on Cholesterol-Enriched diet. *Probiotics Antimicrob Proteins*. 2019;11(2):509-518. doi:10.1007/s12602-018-9429-4
34. Stancu CS, Sanda GM, Deleanu M, Sima AV. Probiotics determine hypolipidemic and antioxidant effects in hyperlipidemic hamsters. *Mol Nutr Food Res*. 2014;58(3):559-568. doi:10.1002/mnfr.201300224
35. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25(5):716-729. doi:10.1038/s41591-019-0439-x
36. Doron S, Snydman DR. Risk and safety of probiotics. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2015;60 Suppl 2(Suppl2):S129-S134. doi:10.1093/cid/civ085
37. Zawistowska-Rojek A, Tyski S. Are probiotic really safe for humans? *Pol J Microbiol*. 2018;67(3):251-258. doi:10.21307/pjm-2018-044