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A Review on the Application of Probiotics in Atherosclerosis Management: Evidence from Preclinical Clinical and Animal Studies

Uma Revisão sobre a Aplicação de Probióticos no Manejo da Aterosclerose: Evidências de Estudos Pré-Clínicos e Clínicos

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Abstract: Atherosclerosis is a chronic vascular disorder characterized by persistent inflammation and the accumulation of atheromatous plaques within the arterial walls, representing a major risk factor for cardiovascular diseases. Emerging evidence suggests that alterations in gut microbiota may influence inflammatory pathways and contribute to the progression of atherosclerosis. This review critically examines the impact of probiotics on atherosclerosis, drawing insights from both preclinical (cellular and animal) and clinical studies. A comprehensive literature search was conducted for studies published between 2010 and 2025 in leading databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Islamic World Science Citation Center (ISC). The search strategy employed a combination of keywords related to "probiotics" and "atherosclerosis." After removing duplicate entries, titles and abstracts were independently screened, and eligible studies were selected according to predefined inclusion criteria. The final selection focused on evidence regarding the effects of probiotics on atherosclerotic processes. Evidence from cellular, animal, and human studies indicates that probiotic strains such as *Lactobacillus* spp., *Bifidobacterium* spp., *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus curvatus*, and *Akkermansia muciniphila* can effectively reduce total cholesterol and LDL levels, increase HDL concentrations, improve endothelial function, and decrease atherosclerotic plaque burden. These benefits are associated with reduced inflammatory markers (IL-6, TNF-α), decreased TMA/TMAO production, inhibition of NF-κB signaling, and modulation of gut microbiota composition. Multi-strain formulations, including Lab4P and VSL#3, not only improve lipid profiles but also enhance plaque stability and reduce foam cell formation. Additionally, the production of beneficial microbial metabolites, such as short-chain fatty acids (SCFAs) and bile acids, along with regulation of cholesterol metabolic pathways, contributes significantly to the anti-atherosclerotic effects of probiotics. By modulating gut microbiota composition as well as metabolic and inflammatory pathways, probiotics demonstrate significant potential to reduce atherosclerotic plaque burden and

associated inflammation. These findings support their role as a promising adjunctive strategy for the prevention and management of atherosclerosis.

Keywords: Probiotics; Atherosclerosis; Gut microbiota; Inflammation; LDL cholesterol; HDL cholesterol

Resumo: A aterosclerose é um distúrbio vascular crônico caracterizado por inflamação persistente e acúmulo de placas ateromatosas nas paredes arteriais, representando um importante fator de risco para doenças cardiovasculares. Evidências emergentes sugerem que alterações na microbiota intestinal podem influenciar vias inflamatórias e contribuir para a progressão da aterosclerose. Esta revisão examina criticamente o impacto dos probióticos na aterosclerose, reunindo dados de estudos pré-clínicos (celulares e animais) e clínicos. Foi realizada uma busca abrangente na literatura para estudos publicados entre 2010 e 2025 em bases de dados relevantes, incluindo PubMed, Scopus, Web of Science, Google Scholar e o Islamic World Science Citation Center (ISC). A estratégia de busca utilizou uma combinação de palavras-chave relacionadas a "probióticos" e "aterosclerose". Após a remoção de duplicatas, os títulos e resumos foram analisados de forma independente, e os estudos elegíveis foram selecionados de acordo com critérios de inclusão predefinidos. A seleção final concentrou-se em evidências sobre os efeitos dos probióticos nos processos ateroscleróticos. Evidências de estudos celulares, animais e humanos indicam que cepas probióticas como *Lactobacillus spp.*, *Bifidobacterium spp.*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus curvatus* e *Akkermansia muciniphila* podem reduzir eficazmente os níveis de colesterol total e LDL, aumentar a concentração de HDL, melhorar a função endotelial e diminuir a carga de placas ateroscleróticas. Esses benefícios estão associados à redução de marcadores inflamatórios (IL-6, TNF-α), diminuição da produção de TMA/TMAO, inibição da sinalização NF-κB e modulação da composição da microbiota intestinal. Formulações multicepas, incluindo Lab4P e VSL#3, não apenas melhoram os perfis lipídicos, mas também aumentam a estabilidade das placas e reduzem a formação de células espumosas. Além disso, a produção de metabólitos microbianos benéficos, como ácidos graxos de cadeia curta (SCFAs) e ácidos biliares, juntamente com a regulação das vias metabólicas do colesterol, contribuem significativamente para os efeitos antiateroscleróticos dos probióticos. Ao modular a composição da microbiota intestinal, assim como vias metabólicas e inflamatórias, os probióticos demonstram potencial considerável para reduzir a carga de placas ateroscleróticas e a inflamação associada. Esses achados sustentam seu papel como uma estratégia adjuvante promissora para a prevenção e manejo da aterosclerose.

Palavras-chave: Probióticos; Aterosclerose; Microbiota intestinal; Inflamação; Colesterol LDL; Colesterol HDL

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Introduction

Chronic diseases represent a growing public health challenge worldwide (BJÖRKEGREN & LUSIS, 2022; ALINEZHAD & KAREGAR, 2016; ALINEZHAD & KAREGAR, 2017). Among these, atherosclerosis is one of the most prevalent and complex cardiovascular disorders (HEMMATI et al., 2021). It is characterized by thickening and stiffening of the arterial walls, impairing blood flow and reducing oxygen delivery to tissues (BJÖRKEGREN & LUSIS, 2022; ALINEZHAD & KAREGAR, 2016; ALINEZHAD & KAREGAR, 2017). Atherosclerosis underlies many major cardiovascular conditions, including myocardial infarction, stroke, and peripheral arterial disease, and remains a leading cause of global mortality (Fan & Watanabe, 2022).

The etiology of atherosclerosis is multifactorial, involving genetic predispositions, environmental influences, and lifestyle factors. Unhealthy dietary habits, obesity, hypertension, diabetes, smoking, and chronic stress are well-established risk factors that contribute to disease onset and progression (RITZ et al., 2014). Pathophysiologically, atherosclerosis begins with endothelial injury, triggering lipid accumulation, atheromatous plaque formation, and persistent vascular inflammation (JEBARI-BENSLAIMAN et al., 2022). The activity of macrophages, vascular smooth muscle cells, and pro-inflammatory mediators further promotes plaque instability and increases the risk of thrombotic events (SAKAKURA et al., 2013).

Complications of atherosclerosis, such as myocardial ischemia, heart failure, stroke, and arterial aneurysms, impose substantial economic and social burdens on healthcare systems (BARTON, 2013). Conventional management strategies include lifestyle modifications, control of blood pressure and glucose, lipid-lowering agents (e.g., statins), antiplatelet therapy, and, in advanced cases, surgical interventions or angioplasty (RICCIONI & SBLENDORIO, 2012). However, given the chronic and inflammatory nature of the disease, there is

growing interest in identifying safe, complementary approaches for its prevention and management (CHARO & TAUB, 2011).

Among these emerging strategies, probiotics have attracted attention for their potential cardiovascular benefits (WILLIAMS, 2010). Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host, primarily by modulating gut microbiota composition (DABBAGHZADEH et al., 2023), reducing systemic inflammation, and regulating lipid metabolism (SOCCOL et al., 2010). Evidence from both preclinical and clinical studies suggests that probiotics may serve as an effective adjunctive approach for preventing and managing cardiovascular diseases, including atherosclerosis, by mitigating risk factors and promoting vascular health (WU & CHIOU, 2021).

This review aims to systematically examine the effects of probiotics on the prevention and treatment of atherosclerosis, consolidating evidence from preclinical (cellular and animal) and clinical studies.

Methods

A literature search was conducted for studies published between 2010 and 2025 in major databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Islamic World Science Citation Center (ISC). The search strategy combined keywords related to “probiotics” and “atherosclerosis” and included terms relevant to both preclinical models (cellular and animal) and clinical studies.

Following initial retrieval, duplicate records were removed, and the remaining titles and abstracts were independently screened by two researchers.

Studies that did not directly address the effects of probiotics on atherosclerosis were excluded.

Inclusion criteria:

- Preclinical (cellular and animal) and human clinical studies evaluating the effects of probiotics on atherosclerosis or related markers, such as vascular inflammation, cholesterol levels, blood pressure, and antioxidant status.
- Articles published between 2010 and 2025.
- Publications in English or Persian.
- Full-text availability.

Exclusion criteria:

- Review or commentary articles lacking original experimental data.
- Studies unrelated to atherosclerosis

or probiotic interventions.

- Articles with incomplete or insufficient data, or without full-text access.
- Duplicate studies or conference reports lacking valid experimental results.

Eligible studies were extracted and synthesized, with particular emphasis on the effects of probiotics on atherosclerosis. This approach enabled a systematic evaluation of both preclinical and clinical evidence.

Results

Human and animal studies consistently demonstrate that probiotic strains, including *Lactobacillus* spp. and *Bifidobacterium* spp., can reduce serum cholesterol, improve dyslipidemia, and decrease vascular inflammation, thereby mitigating the progression of atherosclerosis. In preclinical models, strains such as *Lactobacillus plantarum*, *L. acidophilus*, and *Bifidobacterium animalis* have been shown to lower LDL, total cholesterol (TC), and triglyceride (TG) levels while enhancing endothelial function.

Combination probiotics, such as Lab4P and VSL#3, have been reported in cellular and animal studies to increase HDL levels, reduce plaque burden, attenuate systemic inflammation, and modulate the expression of genes associated with atherosclerosis. Similarly, *Pediococcus acidilactici* R037 and *Lactobacillus rhamnosus* GG inhibit the proliferation of inflammatory cells and restore gut microbiota balance, contributing to reduced vascular inflammation and slowed plaque development.

Additionally, *Akkermansia muciniphila* and formulations combining probiotics with prebiotics have been shown to lower TMAO levels, improve glucose and energy metabolism, and attenuate chronic inflammation, all of which play a crucial role in cardiovascular health.

Overall, the evidence indicates that probiotics exert beneficial effects on lipid profiles, oxidative stress, and endothelial function through modulation of gut microbiota, inflammatory pathways, and metabolic processes. Collectively, these effects contribute to slowing the progression of atherosclerosis. As summarized in Table 1, targeted probiotic interventions may serve as a valuable adjunctive strategy for the prevention and management of atherosclerosis.

Table 1: Effects of Probiotics on Atherosclerosis: Evidence from Preclinical and Clinical Studies

Study	Study Type	Model / Population	Probiotic / Dose	Key Findings	Mechanisms / Notes
HASSAN A et al., 2019	Review	Human, nimal, cellular	*Lactobacillus* & *Bifidobacterium* (10^8–10^{11} CFU/day in humans)	Reduced serum cholesterol and slowed atherosclerosis progression	Decreased intestinal cholesterol absorption, inhibited bile acid reabsorption; regulation of NPC1L1, HMG-CoA reductase, 7α- and 27α-hydroxylase
O'MORAIN & RAMJI, 2020	Review	Human, preclinical	*Lactobacillus* & *Bifidobacterium*	Improved dyslipidemia and vascular inflammation	Modulation of lipid metabolism, reduced inflammation, enhanced endothelial function
ZHAI T et al., 2022	Review	Human, animal, cellular	*Lactobacillus* & *Bifidobacterium* (10^8–10^{11} CFU/day)	Corrected cholesterol imbalance, improved	Macrophage polarization, improved gut

				endothelial function, reduced inflammatory markers	microbiota composition
DIN AU et al., 2019	Review	Human, animal, cellular	*Lactobacillus* & *Bifidobacterium*	Reduced TMA/TMAO production	Modulation of gut microbiota, altered metabolomic profile, miRNA regulation
OYNOTKINOVA et al., 2020	Review	Human, preclinical	*Lactobacillus plantarum* & *Bifidobacterium* combinations	Decreased LDL-C, TC, TG; safe and well-tolerated	Potential adjunctive non-pharmacological therapy
KHALILI L et al., 2023	Meta-analysis	Mouse model	Probiotics & phytochemicals	Reduced atherosclerotic plaque burden	Decreased Firmicutes/Bacteroidetes ratio, increased *Akkermansia muciniphila*
O'MORAIN et al., 2021	Animal	LDLr$^{-/-}$ mice	Lab4P	Increased HDL, reduced LDL/VLDL, reduced plaque inflammation, modulated	Inhibited monocyte/macrophage and vascular smooth muscle migration/proliferation

				gene expression	
NABI XH et al., 2016	Animal	Rabbit	Fermented yogurt cheese (TFCW)	Reduced TC, TG, LDL-C, CRP, VCAM-1, ICAM-1; increased HDL-C	Decreased foam cells, reduced endothelial inflammation; identified 7 *Lactobacillus* and 2 yeast species
MAHDAVI-ROSHAN M et al., 2022	Review	Human, animal	*Lactobacillus* & *Bifidobacterium*	Decreased CRP, TNF-α, IL-6, IL-12, MDA; increased IL-10, TAC, TAS, glutathione, NO	NF-κB pathway inhibition, SCFA and bile acid production
LIANG X et al., 2020	Animal / Cellular	Mouse	*Bifidobacterium animalis* subsp. *lactis* F1-3-2	Reduced serum TMA/TMAO, improved lipid metabolism	Modulation of TMA–TMAO axis, increased CYP7A1 expression, FXR receptor activation
HASSAN A et al., 2020	Animal	ApoE$^{-/-}$ mice	*Lactobacillus plantarum* ATCC 14917	Reduced plaque, oxLDL, MDA,	Inhibited P65 NF-κB signaling, reduced inflammation,

				TNF-α, IL-1β; increased SOD	modulated gut microbiota
AHN HY et al., 2015	Clinical trial	128 non-diabetic hypertriglyceridemic adults	*L. curvatus* HY7601 + *L. plantarum* KY1032, 2 g/day	Reduced TG by 18.3%, increased apo A-V by 21.1%, increased LDL particle size	Improved lipid metabolism, reduced atherosclerosis risk
CHEN L et al., 2013	Animal	ApoE$^{-/-}$ mice	*Lactobacillus acidophilus* ATCC 4356	Reduced plaque, MDA, oxLDL, TNF-α; increased IL-10, SOD	NF-κB inhibition, reduced oxidative stress and inflammation, improved gut microbiota
MIRZOUGHI T et al., 2017	Animal	Mouse	*Pediococcus acidilactici* R037	Reduced atherosclerotic lesions, decreased CD4^{+} T cell proliferation, modulated DCs	Induction of tolerogenic DCs, suppression of Th1 inflammation
HASANI A et al., 2021	Review	Human, animal	*Akkermansia muciniphila*	Reduced aortic lesions and atherosclerosis, improved	Improved metabolic endotoxemia,

				glucose metabolism	enhanced insulin resistance
ZHAI T et al., 2022	Animal	Mouse	*Lactobacillus rhamnosus* GG	Reduced atherosclerotic plaque, improved blood metabolome	Increased beneficial bacteria, elevated blood ketones, reduced endothelial injury
O'MORAIN et al., 2023	In vitro	Cellular	Lab4b	Reduced monocyte/macrophage proliferation and migration, decreased LDL uptake and macropinocytosis	Enhanced cholesterol efflux from foam cells, reduced expression of LDL uptake genes
CAESAR R et al., 2010	Review	Human, animal	Gut microbiota modulation	Reduced inflammation and slowed atherosclerosis progression	Activation of innate immunity, impact on lipid metabolism
MOLOUDI et al., 2018	Review	Human, animal	Probiotics & prebiotics	Reduced TMAO and ECS effects	Modulation of bacterial metabolism and

					atherosclerosis-related pathways
LIU S et al., 2020	Human metagenomics	Fecal samples (Sweden & China)	Gut microbiota profiling	Reduced *Bacteroides xylanisolvens*, *Eubacterium eligens*, *Roseburia inulinivorans* in atherosclerotic patients	Identified potential probiotic targets for therapy

Discussion

Atherosclerosis remains a leading contributor to cardiovascular disease and global mortality, characterized by chronic inflammation and dysregulated lipid metabolism. Emerging evidence highlights the pivotal role of gut microbiota in modulating both inflammatory and metabolic processes associated with atherosclerosis. Within this context, probiotics have emerged as a promising adjunctive intervention, capable of modulating microbial composition and dampening inflammatory responses, thereby potentially slowing disease progression (CRUZ NETO et al., 2024).

Preclinical and review studies indicate that strains of *Lactobacillus* and *Bifidobacterium* exert substantial effects on lipid metabolism, systemic inflammation, and atherosclerotic plaque development. Supplementation with these probiotics has been shown to reduce serum cholesterol, inhibit plaque progression, and improve the LDL/HDL ratio (HASSAN et al., 2019; O'MORAIN & RAMJI, 2020). Key mechanisms underlying these effects include reduced intestinal cholesterol absorption, inhibition of bile acid reabsorption, and modulation of critical lipid biosynthetic pathways, such as HMG-CoA reductase and NPC1L1 (HASSAN et al., 2019; ZHAI et al., 2022).

Animal and cellular studies further demonstrate that probiotics decrease atherogenic metabolites, including TMA and TMAO, enhance lipid metabolism, and suppress NF-κB–mediated inflammatory pathways. These actions result in anti-inflammatory and antioxidant effects, with reductions in reactive oxygen species (ROS) and malondialdehyde (MDA) levels (DIN et al., 2019; HASSAN et al., 2020; LIANG et al., 2020). Probiotics also inhibit monocyte and macrophage migration and proliferation while modulating the expression of genes involved in plaque accumulation and vascular inflammation (O'MORAIN et al., 2021; O'MORAIN et al., 2023).

Clinical evidence corroborates these preclinical findings. For example, a randomized trial by Ahn et al. (2015) demonstrated that administration of a combination of *L. curvatus* HY7601 and *L. plantarum* KY1032 over several weeks led to an 18.3% reduction in triglycerides, a 21.1% increase in apo A-V, and improved LDL particle size, indicating a reduced risk of atherosclerosis. These results underscore the importance of translating preclinical outcomes into human studies and highlight

the need for long-term evaluations of probiotic safety and efficacy.

Another critical aspect of probiotic action lies in their ability to modulate gut microbiota. Human metagenomic studies reveal that individuals with atherosclerosis exhibit reduced abundances of beneficial species, such as *Bacteroides xylanisolvens* and *Roseburia inulinivorans*, which are associated with short-chain fatty acid (SCFA) production and systemic inflammation regulation (Liu et al., 2020). Conversely, increased levels of *Akkermansia muciniphila* are linked to improved insulin sensitivity and decreased metabolic endotoxemia (KHALILI et al., 2023; HASANI et al., 2021).

The synergistic combination of probiotics with phytochemicals or prebiotics further enhances these beneficial effects, outperforming single-strain interventions by reducing atherosclerotic plaque and improving lipid metabolism (MOLOUDI et al., 2018). In animal models, these interventions also demonstrate immune-modulatory effects, including suppression of Th1/Th17 pathways and activation of tolerogenic dendritic cells (MIZOGUCHI et al., 2017).

Taken together, the evidence indicates that probiotics, as a complementary strategy in managing atherosclerosis and related metabolic disorders, confer multiple protective effects. These include reductions in cholesterol and triglycerides, improvements in the LDL/HDL ratio (HASSAN et al., 2019; Oynotkinova et al., 2020), attenuation of inflammation and oxidative stress (MAHDAVI-ROSHAN et al., 2022; CHEN et al., 2013), modulation of gut microbiota with increased SCFA production (CAESAR et al., 2010; ZHAI et al., 2022), lowering of TMA/TMAO levels (Din et al., 2019; Liang et al., 2020), and regulation of immune responses and immune cell migration (O'MORAIN et al., 2021; O'MORAIN et al., 2023).

Despite these promising findings, several critical questions remain, including the determination of optimal doses, treatment duration, probiotic strain composition, and persistence of effects in patients with chronic disease. Future research should focus on well-powered, randomized controlled trials in humans with extended follow-up to fully evaluate the clinical efficacy and safety of probiotics in the context of atherosclerosis (O'MORAIN et al., 2023; LIU et al., 2020).

Conclusion

Probiotics confer significant cardiovascular protective effects through modulation of gut microbiota, lipid metabolism, systemic inflammation, and

atherosclerotic plaque development. Evidence from both preclinical and clinical studies demonstrates that supplementation with *Lactobacillus*, *Bifidobacterium*, and multi-strain formulations can reduce serum cholesterol and LDL levels, increase HDL, improve endothelial function, and slow the progression of atherosclerosis. Furthermore, probiotics decrease TMA/TMAO levels and regulate immune responses, contributing to anti-inflammatory and antioxidant effects. The combination of probiotics with prebiotics or phytochemicals may provide synergistic and more sustained cardiovascular benefits. Collectively, these findings support the role of probiotics as a safe and promising adjunctive strategy for the prevention and management of atherosclerosis. Nevertheless, further research is needed to determine optimal dosages, effective strain combinations, and long-term clinical outcomes in human populations.

Declaration

Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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Authors' Contributions

BA: Conceptualization, data collection, clinical supervision, and draft preparation. BA: Study design, literature review, data interpretation, manuscript writing, and final approval of the version to be published.

Ethical Considerations

The authors have fully adhered to ethical standards, ensuring that no issues related to plagiarism, misconduct, data fabrication, falsification, duplicate publication or submission, or redundancy have occurred.

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