POCZĄTEK, Jakub, PIOTROWSKI, Michał, SERWICKI, Piotr, POŚPIECH, Szczepan, and PROSOWSKI, Jakub. The Role of Gut Microbiota in the Prevention or Development of Atherosclerosis – A Review. Quality in Sport. 2025;40:59609. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2025.40.59609
https://apcz.umk.pl/QS/article/view/59609

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.03.2025. Revised: 26.03.2025. Accepted: 22.04.2025. Published: 22.04.2025.

The Role of Gut Microbiota in the Prevention or Development of Atherosclerosis – A Review

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ABSTRACT

Aim of the study: This study aims to consolidate current knowledge on the role of gut microbiota in atherosclerosis, examining its mechanisms of action, the impact of dietary patterns on microbial composition, and emerging therapeutic interventions.

Materials and methods: A systematic review of scientific literature was conducted through PubMed, Google Scholar, and other databases, focusing on diagnostic advancements, insights into the role of gut microbiota in atherosclerosis, and innovative therapeutic methods.

Main results: The findings reveal that gut microbiota exerts a dual influence on atherosclerosis development through its metabolites, with SCFAs offering anti-inflammatory and cardioprotective effects, while TMAO promotes endothelial dysfunction and pro-thrombotic states. Diet emerges as a critical factor, with fiber-rich and Mediterranean-style diets enhancing SCFA production and reducing TMAO levels, whereas Western diets exacerbate dysbiosis and atherogenesis.

Conclusions: The gut microbiota represents a dynamic and modifiable target for the prevention and management of atherosclerosis. Advancements in diagnostic tools, dietary interventions, and microbiota-based therapies provide new opportunities to address cardiovascular health challenges.

Keywords: Gut microbiota, atherosclerosis, dysbiosis, SCFA, TMAO, probiotics, cardiovascular health

1. INTRODUCTION

The gut microbiota, an intricate community of microorganisms residing in the human gastrointestinal tract, has emerged as a critical player in regulating host metabolic, immune, and cardiovascular health. This dynamic ecosystem is deeply influenced by dietary patterns, environmental factors, and host genetics, with profound implications for the development and progression of chronic diseases such as atherosclerosis and metabolic syndrome [2,8].

In recent years, the interplay between gut microbiota and cardiovascular health has garnered significant attention. Dysbiosis – an imbalance in the composition and function of the gut microbiota – has been linked to systemic inflammation, endothelial dysfunction, and altered lipid metabolism, all of which are central to the pathophysiology of atherosclerosis. Microbial metabolites such as short-chain fatty acids (SCFA) and trimethylamine-N-oxide (TMAO) exemplify the dual role of gut microbiota, acting as both protective and pathogenic mediators depending on their balance and abundance [24].

Diet emerges as a cornerstone in shaping gut microbiota composition and function. Patterns like the Mediterranean diet are associated with enhanced microbial diversity and increased SCFA production, offering protective effects against cardiovascular diseases. Conversely, the Western diet fosters dysbiosis, favoring the production of harmful metabolites like TMAO. These dietary influences underscore the potential for microbiota-targeted interventions, such as probiotics, prebiotics, and dietary modifications, in preventing and managing atherosclerosis [2].

This review aims to provide a comprehensive analysis of the role of gut microbiota in atherosclerosis, focusing on its mechanisms of action, the impact of dietary modulation, and emerging therapeutic strategies. By elucidating these connections, the work seeks to contribute to the growing field of microbiota-based interventions for cardiovascular health.

2. METHODS

A systematic review of scientific and medical literature was conducted using the PubMed and Google Scholar databases. The search focused on the following keywords: "Gut Microbiota" AND "Atherosclerosis" AND "SCFA" AND "TMAO" AND "Cardiovascular Health" AND "Diet." Inclusion criteria included studies on the role of gut microbiota in cardiovascular diseases, mechanisms of dysbiosis, and therapeutic interventions such as probiotics, prebiotics, and dietary modifications. Only studies published from 2015 onwards were included to ensure the use of the most recent data and developments in the field.

This review aims to present updated insights into the relationship between gut microbiota and atherosclerosis, focusing on mechanisms of action, the impact of diet on microbial composition, and emerging therapeutic approaches. Recent scientific findings and clinical practices targeting gut microbiota as a modifiable factor in cardiovascular health were analyzed to provide a comprehensive understanding of its potential role in disease prevention and management.

3. RESULTS AND SUMMARY

The dual role of gut microbiota in cardiovascular health underscores the complexity and potential of microbiota-focused interventions in atherosclerosis management. Research has revealed that microbial composition and function significantly influence systemic inflammation, lipid metabolism, and vascular health. Mechanistic insights into metabolites such as short-chain fatty acids (SCFA) and trimethylamine N-oxide (TMAO) provide a foundation for developing targeted therapeutic strategies. SCFAs, derived from fiber fermentation, exhibit anti-inflammatory properties, enhance gut barrier integrity, and regulate lipid metabolism, demonstrating their cardioprotective effects. Conversely, TMAO, produced from dietary choline and carnitine, exacerbates endothelial dysfunction and pro-thrombotic states, highlighting the need to mitigate its production through microbial modulation.

The impact of dietary patterns on gut microbiota composition further emphasizes the importance of lifestyle modifications in cardiovascular risk reduction. Diets rich in fiber and polyphenols, such as the Mediterranean diet, have been shown to promote SCFA-producing bacteria and suppress TMAO synthesis, offering protective effects against atherogenesis. In contrast, Western-style diets foster dysbiosis, leading to increased cardiovascular risk through the amplification of inflammatory and pro-atherogenic processes.

Emerging therapeutic approaches, including probiotics, prebiotics, and postbiotics, highlight the potential of microbiota-focused interventions. Probiotic formulations targeting beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, have demonstrated efficacy in enhancing microbial diversity and reducing systemic inflammation. Prebiotics, such as inulin and fructooligosaccharides, selectively stimulate beneficial microbial populations, while postbiotics—non-viable bacterial products like SCFA—offer a novel therapeutic avenue with anti-inflammatory and barrier-enhancing properties. Fecal microbiota transplantation (FMT) also holds promise in restoring microbial balance in patients with severe dysbiosis.

Despite these advancements, significant challenges remain. The heterogeneity of microbiota across individuals complicates the prediction of therapeutic outcomes, while regulatory and safety concerns limit the widespread adoption of microbiota-based therapies. Additionally, the integration of microbiota modulation into personalized medicine strategies requires further refinement to maximize efficacy and minimize adverse effects.

In summary, the interplay between gut microbiota and cardiovascular health represents a dynamic and promising field of research. A comprehensive understanding of microbial mechanisms, combined with advancements in dietary and therapeutic interventions, offers new opportunities for reducing the burden of atherosclerosis. Future research should focus on overcoming translational challenges and developing integrated strategies that leverage microbiota modulation to improve cardiovascular outcomes.

4. CONTENT OF THE REVIEW

4.1. MECHANISMS OF GUT MICROBIOTA IN ATHEROSCLEROSIS

The gut microbiota consists of a diverse community of microorganisms that profoundly influence host health, including its metabolic, immune, and cardiovascular systems. These effects are mediated through metabolites such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), which play opposing roles in the development of atherosclerosis. Understanding the composition and functions of the gut microbiota is essential for elucidating its impact on cardiovascular disease.

4.1.1. Composition of Gut Microbiota

The human gut microbiota is composed of several dominant bacterial phyla, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Firmicutes and Bacteroidetes account for over 90% of the gut microbiome in healthy individuals and are essential for maintaining metabolic homeostasis and immune regulation [7, 20]. Specific bacterial genera such as *Faecalibacterium prausnitzii* (Firmicutes) and *Akkermansia muciniphila* (Verrucomicrobia) are recognized for their anti-inflammatory properties and their role in maintaining gut barrier integrity [12, 22].

In dysbiosis, characterized by a reduction in beneficial bacteria and an increase in opportunistic pathogens such as *Escherichia coli* (Proteobacteria), the balance of microbial functions shifts toward pro-inflammatory and pro-atherogenic activities. Dysbiosis has been consistently linked

to increased cardiovascular risk through its impact on inflammation, lipid metabolism, and immune responses [19, 27].

4.1.2. Functions of Gut Microbiota

The gut microbiota influences host health through several mechanisms:

1. ***Immune modulation****:* The microbiota helps maintain immune tolerance by interacting with gut-associated lymphoid tissue (GALT) and regulating the activity of T-regulatory cells. These interactions limit systemic inflammation, a key driver of atherosclerosis [20].
2. ***Metabolic regulation****:* Microbial metabolites such as SCFAs regulate lipid and glucose metabolism, while others, like TMAO, disrupt metabolic homeostasis [25].
3. ***Barrier integrity****:* Beneficial microbes enhance the gut epithelial barrier by producing butyrate, which strengthens tight junctions and reduces endotoxin translocation [12].

4.1.3. Role of SCFA in Atherosclerosis Prevention

SCFAs, including butyrate, propionate, and acetate, are produced by the fermentation of dietary fibers by gut microbiota. These metabolites have demonstrated cardioprotective effects:

- SCFAs exhibit **anti-inflammatory properties** by inhibiting nuclear factor-kappa B (NF-κB) activation and reducing the expression of vascular cell adhesion molecules (VCAM-1), which are critical in monocyte adhesion and foam cell formation, key steps in atherogenesis [17, 27].
- Butyrate plays a pivotal role in enhancing **gut barrier integrity**. By promoting mucosal repair and strengthening tight junctions, it reduces the translocation of lipopolysaccharides (LPS) into the bloodstream, thereby lowering systemic inflammation [12, 20].
- Propionate supports **lipid metabolism regulation** by decreasing hepatic cholesterol synthesis and increasing LDL receptor expression, leading to improved clearance of circulating LDL cholesterol [22].

High-fiber diets, such as the Mediterranean diet, promote the growth of SCFA-producing bacteria like *Faecalibacterium prausnitzii* and *Roseburia spp.*, linking dietary patterns to reduced cardiovascular risk [7, 12].

4.1.4 Role of TMAO in Atherosclerosis Development

TMAO is a pro-atherogenic metabolite derived from trimethylamine (TMA), which is produced by gut bacteria such as *Clostridia* (Firmicutes) and *Escherichia coli* (Proteobacteria) during the

metabolism of dietary choline, phosphatidylcholine, and carnitine. The TMA is subsequently oxidized to TMAO in the liver.

TMAO exacerbates atherosclerosis through multiple mechanisms:

- It promotes **endothelial dysfunction** by inducing oxidative stress and vascular inflammation, impairing the functional integrity of blood vessels [17, 25].
- TMAO increases **cholesterol deposition** in arterial walls by altering cholesterol transport pathways and promoting foam cell formation, which accelerates plaque development [19].
- It enhances **platelet reactivity**, creating a pro-thrombotic environment that elevates the risk of acute cardiovascular events such as myocardial infarction [27].

The contrasting roles of SCFAs and TMAO underscore the dual influence of gut microbiota on atherosclerosis. While SCFAs act as protective agents by reducing inflammation and supporting metabolic health, TMAO amplifies pro-atherogenic processes, highlighting the importance of a balanced gut microbiota composition.

4.2. DYSBIOSIS AND ITS CONSEQUENCES

4.2.1 Definition and Key Features of Dysbiosis

Dysbiosis refers to an imbalance in the composition and function of the gut microbiota. It is characterized by a reduction in beneficial microbial populations, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, alongside an overgrowth of opportunistic and pathogenic species, including *Escherichia coli* and members of the *Clostridia* genus [29]. This microbial imbalance disrupts the intricate interplay between the microbiota and host, leading to compromised metabolic and immune functions. Dysbiosis has been associated with chronic inflammation, increased gut permeability, and a higher risk of metabolic and cardiovascular diseases [6].

4.2.2 Mechanism leading to dysbiosis

Several factors contribute to the development of dysbiosis:

1. ***Antibiotics****:* Overuse of antibiotics disrupts microbial diversity, favoring the dominance of resistant pathogenic strains over beneficial bacteria [14].
2. ***Diet****:* A Western-style diet, rich in fats and sugars but low in dietary fiber, alters microbial composition, reducing SCFA-producing bacteria while promoting TMAO-producing microbes [6, 29].

3. ***Chronic Diseases****:* Conditions like obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) are linked to microbial imbalances that exacerbate systemic inflammation and metabolic dysfunction [9].
4. ***Aging****:* Age-related changes in diet, immunity, and gut physiology further contribute to microbial dysregulation, amplifying the risk of cardiovascular diseases [14].

4.2.3. Consequences of dysbiosis in atherosclerosis and general health

Dysbiosis disrupts the metabolic and immune homeostasis, exacerbating conditions like atherosclerosis through several pathways:

1. ***Increased Endotoxin Translocation*** Dysbiosis compromises the integrity of the gut epithelial barrier, allowing lipopolysaccharides (LPS) and other endotoxins to leak into systemic circulation. These endotoxins activate toll-like receptor (TLR) pathways, triggering systemic inflammation and endothelial dysfunction, which are key drivers of atherogenesis [6, 14].
2. ***Reduced SCFA Production*** Beneficial SCFA-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia spp.*, decline in dysbiosis. This reduces SCFA availability, compromising anti-inflammatory signaling and weakening the gut barrier. Consequently, systemic inflammation and lipid dysregulation are amplified [4, 29].
3. ***Increased TMAO Production*** Pathogenic bacteria like *Clostridia* and *Escherichia coli* dominate in dysbiosis, leading to elevated production of trimethylamine (TMA) from dietary choline and carnitine. TMA is subsequently oxidized in the liver to TMAO, a metabolite known to promote foam cell formation, enhance platelet reactivity, and accelerate atherosclerotic plaque development [29, 30].

4.2.4. Therapeutic implications

a) ***Dietary Modifications***

Increasing dietary fiber intake can stimulate the growth of SCFA-producing bacteria, improving gut microbial diversity. High-fiber diets, such as the Mediterranean diet, have demonstrated benefits in reducing cardiovascular risks by enhancing gut barrier function, suppressing systemic inflammation, and lowering TMAO levels [29, 30].

b) ***Postbiotics***

The use of postbiotics, including SCFAs and other microbiota-derived metabolites, offers promising therapeutic potential. These compounds can inhibit NF-κB signaling, decrease pro-inflammatory cytokine levels, and reinforce gut epithelial integrity,

providing a protective effect against endotoxin translocation and vascular inflammation [3, 9].

c) ***Bile Acid Modulation***

Strategies aimed at correcting dysbiosis-induced bile acid dysregulation can help restore cholesterol metabolism and counteract TMAO-driven cardiovascular risks. Emerging evidence suggests that bile acid-targeted interventions could be instrumental in slowing atherosclerotic progression [4].

d) ***Age-Related Dysbiosis Interventions***

Age-related microbial imbalances demand tailored therapeutic approaches. Personalized interventions, such as probiotics and dietary modifications targeting age-specific microbial changes, could significantly reduce cardiovascular risks in older populations [6, 14].

4.3. DIET AND MICROBIOTA

4.3.1. Influence of diet on gut microbiota composition

Diet is a key factor shaping the composition and diversity of the gut microbiota, with profound implications for metabolic and cardiovascular health. Specific dietary patterns have varying impacts on microbial communities:

- ***Mediterranean Diet****:* Characterized by high intake of fruits, vegetables, whole grains, nuts, and olive oil, this diet supports the growth of beneficial microbes such as *Faecalibacterium prausnitzii* and *Roseburia spp.*, which are associated with anti-inflammatory effects and enhanced SCFA production. It also reduces TMAO synthesis, improving cardiovascular outcomes [2, 29].
- ***Western Diet****:* High in saturated fats, refined sugars, and processed foods, this diet fosters an increase in pathogenic bacteria such as *Escherichia coli* and *Clostridia*, while reducing beneficial SCFA-producing microbes. This shift contributes to dysbiosis, elevated inflammation, and increased cardiovascular risk [6, 26].
- ***Fiber-Rich Diets****:* Dietary fibers promote the fermentation activity of gut microbes, leading to higher SCFA production, improved gut barrier function, and reduced systemic inflammation. These effects are particularly beneficial for mitigating cardiovascular risks [12, 29].

4.3.2 Dietetary components and microbal metabolities

Diet profoundly influences the production of key microbial metabolites that regulate host metabolism and cardiovascular health:

- ***Short-Chain Fatty Acids (SCFA)****:* SCFAs like acetate, propionate, and butyrate are derived from the fermentation of dietary fibers. They exhibit anti-inflammatory effects, enhance lipid metabolism, and strengthen gut barrier integrity. Fiber-rich diets significantly increase SCFA production, reducing cardiovascular risks [1, 11].
- ***Trimethylamine N-Oxide (TMAO)****:* TMAO is produced from dietary choline and carnitine through microbial pathways involving *Clostridia* and *Escherichia coli*. High TMAO levels, promoted by a Western diet, contribute to endothelial dysfunction, oxidative stress, and the development of atherosclerosis [25, 26].
- ***Pathways Linking Microbial Metabolites and Cardiovascular Health****:* Emerging evidence highlights the role of specific gut microbial pathways in modulating cardiovascular health. SCFA-producing pathways are protective against inflammation and dyslipidemia, while TMAO-related pathways exacerbate atherosclerotic progression [32].

4.3.3. Dietary interventions for microbiota modulation

1. ***Probiotics****:* Probiotics, such as *Lactobacillus* and *Bifidobacterium* strains, enhance gut microbial diversity, suppress pathogenic bacteria, and increase SCFA production. Clinical studies show that probiotics reduce TMAO levels and mitigate systemic inflammation, contributing to improved cardiovascular health [5, 21].
2. ***Prebiotics****:* Prebiotics, including inulin and fructooligosaccharides, selectively promote the growth of beneficial bacteria. They enhance SCFA levels, restore gut barrier integrity, and counteract dysbiosis, complementing the effects of probiotics [26, 32].
3. ***Fecal Microbiota Transplantation (FMT)****:* FMT involves the transfer of gut microbiota from a healthy donor to a dysbiotic recipient. This intervention has shown promise in restoring microbial diversity, reducing TMAO synthesis, and mitigating dysbiosis-associated cardiovascular risks [10, 28].

4.3.4. Conclusion

Dietary patterns play a central role in modulating gut microbiota composition and metabolic activity. While a Mediterranean diet and fiber-rich foods enhance beneficial SCFA production, reduce systemic inflammation, and improve cardiovascular health, a Western diet promotes dysbiosis and TMAO synthesis, heightening cardiovascular risks. Dietary interventions,

including probiotics, prebiotics, and fecal microbiota transplantation, represent promising strategies to restore microbial balance and mitigate atherosclerosis risk.

4.4. RESEARCH PROSPECTIVES

4.4.1. Targeting gut microbal pathways

The modulation of gut microbial pathways offers significant promise in addressing the complex interactions between microbiota and cardiovascular health. Recent studies highlight the potential of targeting specific microbial pathways, such as SCFA synthesis and TMAO production, to mitigate atherosclerosis progression. For instance, interventions that enhance SCFA-producing bacteria through diet or probiotics have been shown to reduce inflammation and improve lipid metabolism. [33] Similarly, inhibiting TMA production by targeting microbial enzymes could provide a novel therapeutic approach to reducing TMAO-associated risks. [23]

4.4.2. Precision medicine and probiotic innovations

Precision medicine strategies integrating microbiota data are paving the way for targeted therapies. Advances in sequencing technologies allow for individualized microbial profiling, enabling the development of tailored probiotic formulations. Probiotic strains such as *Enterococcus faecium* and *Lactobacillus rhamnosus* have demonstrated efficacy in reducing atherosclerosis through SCFA production and inflammation reduction. [33, 31] Furthermore, engineered probiotics that deliver specific metabolites or inhibit pathogenic bacteria are under investigation as next-generation solutions. [13]

4.4.3. Dietary modulation and postbiotic applications

Dietary interventions remain a cornerstone of microbiota modulation. Diets enriched in fibers, polyphenols, and prebiotics enhance beneficial microbial populations and their metabolites, including SCFA, which protect against vascular damage. [15, 16] Postbiotics—non-viable bacterial products such as SCFA or microbial peptides—are emerging as potent therapeutic agents. These compounds have been shown to suppress inflammation and improve endothelial function, offering benefits comparable to live probiotics without the need for viable bacterial delivery. [33, 18]

4.4.4. Metagenomics and diagnostic advancements

Metagenomic tools are revolutionizing the diagnostic landscape, enabling comprehensive analysis of the gut microbiota's genetic potential. By identifying microbial signatures associated with cardiovascular diseases, metagenomics facilitates early diagnosis and treatment

customization. Biomarkers derived from gut microbiota, such as specific SCFA profiles or TMAO levels, are being explored as non-invasive diagnostic tools. [23, 13]

4.4.5. Challenges and opportunities in clinical translation

Despite promising advancements, translating microbiota-based therapies to clinical practice faces several challenges:

- ***Interindividual Variability**:* Microbiota composition varies widely among individuals, complicating the prediction of therapeutic outcomes. [16]
- ***Safety and Efficacy**:* Ensuring the safety of novel interventions, such as engineered probiotics or FMT, remains a critical barrier. [31]
- ***Regulatory Frameworks**:* Standardizing protocols and regulatory pathways for microbiota-based therapies is essential for their broader clinical adoption. [15, 33]

However, these challenges present opportunities for innovation in personalized medicine, long-term efficacy studies, and interdisciplinary collaboration.

4.4.6. Toward integrated therapeutic strategies

Integrating dietary, pharmacological, and microbial-based approaches offers a holistic strategy for managing cardiovascular diseases. Combining prebiotics with tailored probiotics, or utilizing postbiotics alongside traditional therapies, could enhance outcomes by addressing both systemic inflammation and microbiota dysbiosis. Future therapeutic strategies will likely incorporate microbiota modulation as a cornerstone of cardiovascular care. [31, 18]

5.CONCLUSIONS AND SUMMARY

The gut microbiota is a dynamic and essential regulator of host metabolic, immune, and cardiovascular health, playing a dual role in the pathogenesis and prevention of atherosclerosis. Dysbiosis, characterized by a reduction in beneficial microbial populations and an overgrowth of pathogenic species, disrupts systemic homeostasis, driving inflammatory processes, endothelial dysfunction, and altered lipid metabolism. At the same time, beneficial metabolites like short-chain fatty acids (SCFA) exhibit anti-inflammatory and cardioprotective effects, while harmful metabolites such as trimethylamine N-oxide (TMAO) exacerbate pro-atherogenic pathways.

Dietary patterns emerge as pivotal modulators of gut microbiota composition and function. Fiber-rich diets, particularly the Mediterranean diet, foster the growth of SCFA-producing bacteria, enhancing gut barrier integrity and reducing systemic inflammation. In contrast, Western diets high in saturated fats and refined sugars exacerbate dysbiosis and promote the

production of pathogenic metabolites. These dietary influences underline the critical role of lifestyle modifications in mitigating cardiovascular risks.

Emerging therapeutic strategies, including probiotics, prebiotics, postbiotics, and fecal microbiota transplantation (FMT), offer significant promise in restoring microbial balance and mitigating the impact of dysbiosis on cardiovascular health. Probiotics and prebiotics can selectively enrich beneficial microbial populations, while postbiotics provide direct therapeutic effects through anti-inflammatory and barrier-enhancing properties. FMT presents a novel approach for severe dysbiosis, demonstrating potential for significant microbial ecosystem restoration.

Despite these advancements, challenges persist in translating microbiota-targeted therapies into clinical practice. Interindividual variability in microbiota composition complicates the predictability of therapeutic outcomes, while safety concerns and regulatory barriers limit widespread adoption. Moreover, the integration of microbiota modulation into precision medicine requires further refinement to ensure efficacy and safety across diverse patient populations.

In conclusion, the gut microbiota offers a promising and modifiable target for improving cardiovascular health. Advances in microbiota-focused diagnostics, dietary interventions, and therapeutic applications have the potential to revolutionize the prevention and management of atherosclerosis. Addressing translational challenges through collaborative, interdisciplinary research will be key to unlocking the full potential of microbiota modulation in clinical settings. Future efforts should focus on personalized approaches, integrating microbiota-based strategies with existing therapeutic protocols to provide comprehensive cardiovascular care.

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Funding acquisition: not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding Statement:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict of Interest Statement:

Authors have declared no conflict of interests.

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