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Molecular and clinical interactions between gut microbiota and endothelial dysfunction: A review of mechanisms and therapeutic perspectives

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ABSTRACT

Cardiovascular diseases remain the leading cause of mortality worldwide, accounting for approximately 32% of all deaths recorded in 2022, according to data provided by the World Health Organization. Although traditional risk factors are well known, a significant proportion of residual cardiovascular risk remains unexplained. Over the last decade, the gut microbiota has gained interest as an essential regulator of metabolic and immune homeostasis, and the concept of "gut-heart axis" has gained increasing attention in medical literature. This review aims to synthesize the current evidence we have linking gut dysbiosis to endothelial dysfunction in various vascular pathologies. It will analyze the molecular mechanisms through which microbiota-derived metabolites such as trimethylamine-N-oxide (TMAO), short-chain fatty acids, and bacterial lipopolysaccharides modulate nitric oxide bioavailability, vascular inflammation, and oxidative stress. Furthermore, the paper discusses the clinical implications of these interactions and the potential of therapeutic strategies based on microbiome modulation through probiotics, prebiotics, or fecal transplant in restoring proper endothelial function. Understanding the complexity of this axis and the gut-heart interactions offers valuable insights for personalized medicine and cardiovascular prevention. This review brings novelty by integrating recent molecular and clinical evidence on the gut-heart axis, highlighting microbiota-derived metabolites as potential therapeutic targets.

Keywords: gut microbiota, endothelial dysfunction, gut-heart axis, TMAO, short-chain fatty acids, inflammation, cardiovascular risk, microbiome therapy

INTRODUCTION

The vascular endothelium was long considered a simple, inert, physical barrier separating blood from extravascular tissues. Today, however, it is appreciated as one of the most intricate and active endocrine organs in the human body. With an estimated total surface area of 3,000-6,000 m^2 [1], the endothelium plays a central role in regulating vascular tone, blood fluidity, inflammatory response, and angiogenesis [2]. Endothelial dysfunction is characterized by the shift from a "quiescent" or a silent phenotype to a pro-inflammatory, pro-thrombotic, and vasoconstrictive one. This shift constitutes the early and obligatory event in the development of atherosclerosis and arterial hypertension (HTN), preceding clinical manifestations by years or even decades [3].

The defining agent of endothelial function is nitric oxide (NO), a signaling gas molecule synthesized from the amino acid L-arginine under the action of an endothelial enzyme called NO synthase (eNOS). A decrease in NO synthesis or its rapid inactivation by oxidative stress constitutes the biochemical hallmark of endothelial dysfunction [4]. Although classic risk factors such as dyslipidemia, diabetes mellitus, smoking, or hypertension, etc. are well-known and well-studied causes of endothelial injury, recent studies suggest the existence of alternative pathogenic mechanisms, independent of these risk factors.

One such mechanism that has become a major interest point of recent research is the influence of gut microbiota in various cardiovascular pathologies and even beyond. The gut microbiota can be defined as a complex community consisting of trillions of microorganisms that colonize and influence the gastrointestinal tract. The collective genome of the microbiota exceeds the human genome by over 100 times, supplying the host with advanced metabolic capabilities [5]. In a state of good health also known as eubiosis, the microbiota contributes with energy extraction from food, vitamin synthesis, and maintenance of intestinal barrier integrity. However, when the composition of this extended ecosystem is altered, the state becomes known as dysbiosis, which has been associated with the development of extra-intestinal pathologies, including metabolic and cardiovascular diseases.

The gut-heart axis postulates the existence of bidirectional communication between the microbiome and the cardiovascular system, mediated by bioactive metabolites entering systemic circulation. The intestinal barrier plays a

critical role through increased intestinal permeability, a phenomenon known as “leaky gut” syndrome. Leaky gut allows the translocation of bacterial components such as lipopolysaccharides (LPS) and other toxic metabolites into the blood, triggering a systemic inflammatory reaction directly targeting the vascular endothelium. Moreover, recent studies have identified specific flora-dependent metabolites, such as trimethylamine-N-oxide (TMAO), as potential predictors of cardiovascular mortality, directly influencing endothelial cells to promote leukocyte adhesion and atheroma plaque formation [6].

Despite the growing body of evidence linking gut microbiota to cardiovascular diseases, important gaps remain regarding the precise molecular mechanisms underlying endothelial dysfunction and the translational applicability of these findings. Moreover, recent high-impact studies (2024-2025) highlight the need for a more integrative perspective combining microbiome-derived metabolites, host response, and therapeutic modulation. Therefore, this review aims to provide a comprehensive, up-to-date synthesis of current knowledge while addressing research gaps.

MATERIALS AND METHODS

For the realization of this review, an extensive search was conducted in specialized medical literature within major scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar. The documentation process covered the period between 2005 and 2025, with a particular emphasis on articles published in the last 5 years (2020-2025), to capture the most recent discoveries in the field. Particular emphasis was placed on high-impact publications from 2024-2025 to ensure that the review reflects the most recent advances in the field.

The research strategy consisted of combinations of keywords “gut microbiota”, “endothelial dysfunction”, “gut-heart axis”, “TMAO”, “inflammation”, “atherosclerosis”, “dysbiosis”, using Boolean operators “AND” and “OR”. The final selection of the bibliography was made based on scientific relevance and methodological quality of the studies, aiming to offer a balanced and up-to-date overview of the gut-heart axis.

PATHOPHYSIOLOGY: MOLECULAR MECHANISMS OF GUT-ENDOTHELIUM INTERACTION

Despite the apparent anatomical separation, the gut and the vascular system communicate permanently through a complex signaling network. This communication is not mediated by direct contact, but through bioactive metabolites and bacterial components that manage to cross the intestinal barrier. Recent studies have shown that microbiota-induced endothelial dysfunction is the result of an imbalance between protective and aggressive factors.

Altered Intestinal Barried, Endotoxemia, and TLR4 Axis

The intestinal barrier represents the body’s first line of defense. It is comprised of a mucus layer, epithelial cells connected by tight junctions, and immune cells in the lamina propria. Tight junctions are constituted of proteins such as occludin, claudins, and zonula occludens-1 (ZO-1) [7]. Under dysbiosis conditions, the expression of these junction proteins decreases, leading to the “leaky gut” syndrome.

Leaky gut allows the translocation into the portal circulation, but especially into the systemic circulation, of bacterial wall components, particularly LPS. LPS are major structural components of the outer membrane of Gram-negative bacteria such as *Escherichia coli* or *Bacteroides spp*. The long-term presence of low but pathological levels of LPS in the blood defines the concept of metabolic endotoxemia [8].

Once arrives in the blood flow, LPS binds to the lipopolysaccharide-binding protein, and this complex activates the Toll-like receptor 4 (TLR4) expressed on the surface of endothelial cells. TLR4 activation triggers an intracellular signaling cascade mediated by nuclear factor κB (NF-κB).

Nuclear translocation of NF-κB induces the transcription of pro-inflammatory genes, with major consequences on endothelial function. Among these consequences is the expression of adhesion molecules. This is achieved by increasing the synthesis of vascular cell adhesion molecule 1, favoring monocyte adhesion to the vascular wall. Subsequently, cytokine synthesis begins with the release of IL-6, IL-1β, and TNF-α, factors that amplify local and systemic inflammation. TLR4 activation also leads to increased production of reactive oxygen species (ROS). ROS react rapidly with NO, forming peroxynitrite ($ONOO^-$), a powerful oxidant that not only nullifies the vasodilator effect by reducing NO bioavailability but also induces eNOS uncoupling, thus transforming this enzyme from a NO producer into a potent generator of superoxide, harmful to normal vascular function [9].

Trimethylamine-N-Oxide

Gut microbiota possesses specific enzymes (choline-TMA lyases) that cleave the C-N bond of these nutrients, generating trimethylamine (TMA), a gas with a specific odor. TMA is rapidly absorbed into the portal circulation and transported to the liver. Here, enzymes from the hepatic flavin-monooxygenase family oxidize TMA, forming TMAO ([10].

Unlike its precursors, TMAO is not a simple waste product, but an active mediator of endothelial dysfunction. Elevated plasma levels of TMAO significantly affect the endothelium by decreasing NO synthesis and promoting endothelial cell senescence.

Clinical studies have confirmed that high circulating levels of TMAO are predictors for major cardiovascular events such as myocardial infarction or stroke, even after adjusting for traditional risk factors [11].

Recent evidence further supports the role of TMAO as both a biomarker and a mechanistic contributor to cardiovascular disease. A 2025 systematic review and dose-response meta-analysis demonstrated that elevated circulating TMAO levels are independently associated with an increased risk of major adverse cardiovascular events following percutaneous coronary intervention. Moreover, emerging data suggest that TMAO contributes to endothelial dysfunction through inflammatory activation, oxidative stress, altered lipid metabolism, and thrombotic pathways, reinforcing its role as a promising therapeutic target within the gut-heart axis [12, 13].

Short-Chain Fatty Acids

The metabolism of indigestible dietary fibers by commensal bacteria, belonging particularly to the genera of *Faecalibacterium*, *Roseburia*, and *Bifidobacterium*, generates metabolites with significant beneficial effects on the host, unlike TMAO. These metabolites, called short-chain fatty acids (SCFAs), are not only an energy source for colonocytes, but they also enter systemic circulation and act through complex mechanisms as signaling molecules protecting the endothelium.

One such mechanism is represented by the activation of G-protein-coupled receptors (GPCRs). SCFAs are natural ligands for receptors expressed at the level of vascular endothelial cells. Activation of these receptors induces direct vasodilation, contributing to blood pressure reduction. One study demonstrated that SCFAs mediate the release of vasodilatory prostaglandins, counteracting the vasoconstrictive effects of angiotensin II [14].

Another sophisticated mode of action characteristic to SCFAs constitutes the inhibition of histone deacetylases (HDACs). Under normal circumstances, HDACs keep the chromatin structure compact, suppressing the expression of certain genes. SCFAs, especially butyrate, act as potent inhibitors of HDACs and thus relax the chromatin structure in endothelial cells, allowing the transcription of genes encoding antioxidant enzymes. Furthermore, butyrate reactivates the gene expressing eNOS, increasing NO production and restoring the barrier function of the endothelium [15].

Recent studies have expanded the understanding of SCFA-mediated cardiovascular protection. Beyond their local effects on intestinal barrier integrity, SCFAs act as systemic immunometabolic regulators, modulating endothelial homeostasis through GPCR signaling and epigenetic regulation. Current evidence indicates that reduced SCFA availability is consistently associated with endothelial dysfunction, hypertension, and increased cardiovascular risk, highlighting these metabolites as key mediators linking dietary fiber intake to vascular health [13, 16].

Secondary Bile Acids and Tryptophan Metabolites

The interaction between the liver and the intestine generates secondary bile acids that have a profound impact on vascularisation. Primary bile acids (cholic and chenodeoxycholic acid) are converted by colonic microbiota into secondary bile acids (deoxycholic and lithocholic acid). These metabolites act on two important receptors present in the vascular system: the farnesoid X receptor (FXR) and the TGR5 receptor.

FXR activation at the endothelial level increases eNOS expression and reduces the level of potent vasoconstrictors such as endothelin-1. However, this balance is fragile as certain studies suggest that an excess of hydrophobic secondary bile acids can be toxic to endothelial cells. Activation of the TGR5 membrane receptor by secondary bile acids induces NO release and has anti-atherosclerotic effects, inhibiting the formation of “foamy cells” from macrophages [7].

Another notable example is tryptophan metabolism. Intestinal bacteria convert dietary tryptophan into indole derivatives. These compounds are ligands for the aryl hydrocarbon receptor (AhR) [18]. Activation of AhR in the endothelium reduces cytokine-induced inflammation and promotes vascular integrity, demonstrating yet another pathway by which a healthy microbiota can represent a solid protective factor against atherosclerosis.

MICROBIOTA AND PATHOLOGIES ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION

The alteration of efficient bidirectional communications within the gut-cardiovascular system axis does have clinical consequences. Epidemiological and experimental evidence from the last 5 years has outlined specific “microbial signatures” associated with the main endothelial dysfunction pathologies.

Arterial Hypertension

Arterial HTN is often the first clinical manifestation of endothelial dysfunction. Metagenomic studies have highlighted a significant decrease in the diversity and richness of beneficial bacterial species in hypertensive patients compared to normotensive ones.

Furthermore, fecal matter transplant (FMT) experiments have brought proof of this association. In conducted experiments, healthy germ-free mice that received fecal matter from hypertensive human donors developed elevated blood pressure values, accompanied by vascular inflammation. The mechanism implies the depletion of SCFA-producing bacteria. Thus, the absence of butyrate and propionate reduces the stimulation of endothelial receptors and limits vasodilation. In parallel, an increase in the abundance of opportunistic genera such as *Klebsiella* and *Prevotella* was positively correlated with high systolic blood pressure values [19].

Atherosclerosis and Plaque Instability

The gut microbiota intervenes in the progression of atheroma plaque not only through systemic inflammation but also through distal colonization. Recent studies using 16S rRNA sequencing identified bacterial DNA inside carotid atheroma plaques having a taxonomic composition similar to that in the intestine of the same patient, suggesting active translocation of bacteria through a compromised intestinal barrier [20, 21].

A major protective role belongs to the bacterium *Akkermansia muciniphila*. This species resides in the intestinal mucus layer and is inversely correlated with obesity and atherosclerosis. By maintaining mucus layer thickness and tight junction integrity, *A. muciniphila* prevents diet-induced metabolic endotoxemia, thus reducing macrophage infiltration into the arterial wall and the risk of plaque rupture [22].

Type 2 Diabetes Mellitus and Insulin Resistance

The endothelium and glucose metabolism are closely linked as insulin is an endothelium-dependent vasodilator through eNOS stimulation. In type 2 diabetes mellitus (T2DM), this pathway is blocked, leading to insulin resistance. Dysbiosis in T2DM is characterized by a decrease in butyrate-producing bacteria and an increase in opportunistic pathogens possessing strong pro-inflammatory activity.

LPS originating from the gut activate TLR4 receptors not only at vascular level but also in adipocytes and hepatocytes, generating a state of extensive chronic inflammation. This blocks insulin receptor signaling, creating a vicious circle

wherein hyperglycemia induces endothelial dysfunction, which in turn aggravates insulin resistance [23].

THERAPEUTIC STRATEGIES: MODULATION OF MICROBIOTA FOR RESTORATION OF ENDOTHELIAL FUNCTION

Given the essential role of dysbiosis in cardiovascular pathogenesis, restoring eubiosis represents a promising therapeutic approach. Current strategies vary from non-invasive nutritional interventions to direct manipulation of the intestinal ecosystem.

Nutritional and Dietary Interventions

Of all studied dietary models, the Mediterranean diet has demonstrated some of the most consistent benefits on the gut-heart axis and overall health status. Rich in fiber, monounsaturated fatty acids, and polyphenols, this diet favors the proliferation of saccharolytic species such as *Bifidobacterium* and *Lactobacillus* to the detriment of proteolytic ones [24].

Among the multiple beneficial mechanisms highlighted in following the Mediterranean diet is the increased production of SCFAs. The high intake of indigestible complex carbohydrates offers a substrate for bacterial fermentation, generating butyrate, which maintains intestinal barrier integrity and reduces systemic inflammation. Also, polyphenols from olive oil, fruits, and red wine manage to reduce bioavailability in the small intestine. Reaching the colon, they are metabolized by the microbiota into bioactive phenolic compounds with superior antioxidant properties, protecting the endothelium from oxidative stress [25]. A plant-based diet naturally reduces the intake of choline and carnitine. Moreover, it has been observed that in vegetarians, even occasional administration of carnitine does not lead to a significant increase in TMAO, suggesting that their microbial profile has adapted to not generate this toxic metabolite [26, 27].

Probiotics and Prebiotics

Probiotics represent live microorganisms that offer various benefits to the host. Their administration in medical practice has shown promising, though heterogeneous, results in clinical trials. Recent meta-analyses indicate that supplementation with specific strains of *Lactobacillus,* such as *L. casei* or *L. plantarum,* and various *Bifidobacterium* species can modestly but significantly reduce systolic and diastolic blood pressure, the effect being more pronounced in patients with high baseline values. Mechanisms include hydrolysis of bile salts and production of bioactive peptides having similar action to angiotensin-converting enzyme inhibitors [28].

Prebiotics such as inulin or fructo-oligosaccharides selectively stimulate the growth of beneficial bacteria. By measuring flow-mediated dilation, it was shown that inulin supplements improve endothelial function in patients with diabetes mellitus, correlating with decreased levels of plasma LPS [29, 30].

Fecal Microbiota Transplantation

FMT, established in the treatment of recurrent *Clostridioides difficile* infection, is experimentally explored for metabolic diseases.

Randomized controlled trials have shown that microbiota transfers from normal-weight or even underweight donors to patients with metabolic syndrome can temporarily increase insulin sensitivity [31].

However, the applicability of FMT in chronic cardiovascular diseases remains limited due to safety risks and a lack of standardization.

Novel Pharmacological Targets

A much more promising direction is “microbiota pharmacology”. Researchers have developed specific inhibitors of bacterial enzymes that do not have a bactericidal role but block the harmful function and thus avoid antibiotic resistance [32, 33]. An example of such inhibitor is 3,3-dimethyl-1-butanol (DMB), a structural analog of choline found in olive oil and balsamic vinegar. DMB inhibits the bacterial TMA-lyase enzyme, preventing TMA formation and, implicitly, TMAO, thus attenuating atherosclerosis development in murine models without affecting intestinal flora viability [34, 35]. This approach opens the way towards a new class of cardiovascular drugs targeting the microbiome, not the host.

Recent advances in microbiome-targeted therapies have shifted the focus from broad microbial manipulation to precision interventions aimed at specific microbial pathways. Novel approaches include enzyme inhibitors targeting TMA production, personalized dietary modulation, next-generation probiotics, and multi-omics-guided microbiome interventions. These strategies aim to preserve beneficial microbial functions while selectively reducing the production of harmful metabolites associated with cardiovascular disease [36].

The Influence of Cardiovascular Medications

Although traditionally viewed through the lens of their primary systemic effects, widely prescribed cardiovascular medications such as statins and diuretics exert profound influences on both gut absorption and the composition of the intestinal microbiota, thereby indirectly modulating endothelial function.

Statins

Statins, also known as HMG-CoA reductase inhibitors, are generally used to reduce blood cholesterol levels. Moreover, they are also recognized for their potent pleiotropic effects, which include the modulation of systemic inflammation and macrophage proliferation. Statin therapy helps maintain gut microbiota homeostasis, significantly reducing the prevalence of gut dysbiosis. This class of medications actively alters the gut microbiota, enhancing the production of beneficial microbial-derived metabolites, particularly SCFAs, and regulating both primary and secondary bile acids [37]. The increase in SCFAs provides essential protection by maintaining the integrity of the intestinal barrier, thus mitigating “leaky gut” syndrome, and promoting direct endothelial protection.

The relationship between statins and the microbiome is strongly bidirectional. Gut microbiota can actually downgrade or modify statins, a process that directly impacts drug pharmacokinetics and clinical effectiveness. Clinical studies even suggest that the co-administration of probiotics could enhance the efficacy of statins in reducing hypercholesterolemia and vascular inflammation. Understanding this complex interaction opens up highly promising directions for personalized medicine and novel therapeutic targets in cardiovascular care [38, 39].

Diuretics

Diuretics, including thiazides and loop diuretics, represent cornerstone therapies for the managements of HTN and heart failure. While these medications effectively lower blood pressure and manage fluid overload, recent evidence indicates that they can also disrupt gut microbiota homeostasis. For instance, hydrochlorothiazide (HCTZ) consumption can disturb the structure of the intestinal microbiota, causing an abnormal elevation of Gram-negative bacteria such as *Enterobacteriaceae* and LPS, which may lead to intestinal barrier dysfunction [40].

However, the interaction between diuretics and the gut microbiome is highly context-dependent. In patients with chronic heart failure, loop diuretics play a crucial role in relieving intestinal mucosal congestion and bowel edema. By reducing this localized fluid retention, diuretics help restore normal gut wall integrity, limit the “leaky gut” syndrome, and reduce the systemic translocation of toxic endotoxins and inflammatory mediators into the bloodstream [41].

Furthermore, co-administering diuretics like HCTZ with specific probiotics like *Limosilactobacillus fermentum* CECT5716 can remarkably potentiate their protective effects on endothelial dysfunction. This co-administration normalizes microbiota alterations, such as reducing the *Firmicutes/Bacteroidota* ration and suppressing LPS biosynthesis, ultimately improving the antihypertensive response and offering superior endothelial protection [42].

FUTURE DIRECTIONS

Although current studies have shown promising results, the subject is not sufficiently explored yet. A transition from cross-sectional studies to long-term longitudinal and cohort studies is necessary to see if microbiota changes preceded endothelial dysfunction or whether they are a consequence. Standardization of interventions is also necessary as there is no clear definition of combinations, doses, or probiotic strains effective for hypertension and atherosclerosis.

Personalized medicine is a branch gaining rapid interest among clinicians as, in this case, the use of microbiome profiling as a routine biomarker is taken into consideration. In the future, cardiovascular risk assessment parameters could include, besides cholesterol and glycemia, plasma TMAO dosing or fecal microbiota sequencing.

Integrating gut microbiota into the cardiovascular risk equation opens new therapeutic horizons. Although a standard procedure or prescription has not yet been finalized, optimizing diet and lifestyle to nourish a friendly microbiome remains, for now, the most effective strategy for maintaining endothelial health.

The present review integrates current evidence regarding the bidirectional relationship between gut microbiota and endothelial dysfunction, highlighting both converging and divergent findings across studies. While numerous experimental studies consistently demonstrate the detrimental role of metabolites such as TMAO in promoting oxidative stress and vascular inflammation, clinical data remain partially inconsistent due to population heterogeneity and methodological variability. Compared to previous studies, our findings support the hypothesis that microbiota-derived metabolites exert both protective (e.g., SCFAs) and harmful (e.g., LPS and TMAO) effects, depending on microbial composition and host metabolic context. Similar observations have been reported in recent studies (2024-2025), emphasizing the dual role of the microbiome in cardiovascular homeostasis. Furthermore, discrepancies between animal models and human studies must be carefully interpreted. While murine models provide mechanistic insights, their translational applicability is limited by differences in diet, microbiota composition, and metabolic regulation. Overall, these findings reinforce the concept that endothelial dysfunction is not solely a consequence of classical risk factors but also a result of complex host-microbiome interactions, necessitating complex, individualized therapeutic approaches.

Study Limitations

This review has several limitations that should be acknowledged. First, a significant proportion of the included evidence is derived from experimental and animal studies, which may limit direct clinical extrapolation. Second, heterogeneity in study design, population characteristics, and microbiota analysis techniques may introduce variability in reported outcomes. Third, the lack of standardized protocols for microbiome assessment and intervention limits the comparability of results across studies. Finally, although recent literature was prioritized, rapid advancements in this field may lead to emerging data not yet fully integrated into current interpretations.

CONCLUSIONS

The coining and elaboration of the gut-heart axis concept have fundamentally changed the paradigm in preventive medicine. The evidence presented in this review emphasizes that gut microbiota is not a passive component, but an active metabolic organ modulating endothelial function through fine and even sophisticated mechanisms.

The transition from eubiosis to dysbiosis functions as a metabolic “switch” that can trigger pro-atherogenic cascades through metabolic endotoxemia due to LPS influence or diet-dependent metabolites via TMAO action. Maintaining a diverse, upright microbial population capable of producing SCFAs and of metabolizing bile acids constitutes an endogenous vascular protection mechanism, maintaining NO bioavailability and endothelial barrier integrity at optimal parameters.

However, translating these findings from the laboratory to the clinic still faces challenges. Most data provided by research come from murine models, and human studies are predominantly observational, making it difficult to establish firm causality in genetically and dietetically heterogeneous populations.

Beyond summarizing current knowledge, these findings highlight the potential of microbiome-targeted interventions as innovative strategies for cardiovascular risk reduction. Future clinical applications may include personalized microbiome modulation, targeted inhibition of harmful metabolites, and integration of microbiota profiling into routine cardiovascular risk assessment.

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REFERENCES

1. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: An update. Int J Mol Sci. 2019;20(18):4411. https://doi.org/10.3390/ijms20184411 PMid:31500313 PMCid:PMC6769656
2. Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res. 2016;118(4):620-36. https://doi.org/10.1161/CIRCRESAHA.115.306301 PMid:26892962 PMCid:PMC4762052
3. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction. Circulation. 2007;115(10):1285-95. https://doi.org/10.1161/CIRCULATIONAHA.106.652859 PMid:17353456
4. Förstermann U, Sessa WC. Nitric oxide synthases: Regulation and function. Eur Heart J. 2012;33(7):829-37. https://doi.org/10.1093/eurheartj/ehr304 PMid:21890489 PMCid:PMC3345541
5. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. https://doi.org/10.1371/journal.pbio.1002533 PMid:27541692 PMCid:PMC4991899
6. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470-81. https://doi.org/10.2337/db07-1403 PMid:18305141
7. Kuo WT, Odenwald MA, Turner JR, Zuo L. Tight junction proteins occludin and ZO-1 as regulators of epithelial proliferation and survival. Ann N Y Acad Sci. 2022;1514(1):21-33. https://doi.org/10.1111/nyas.14798 PMid:35580994 PMCid:PMC9427709
8. Chmielarz M, Sobieszczańska B, Środa-Pomianek K. Metabolic endotoxemia: From the gut to neurodegeneration. Int J Mol Sci. 2024;25(13):7006. https://doi.org/10.3390/ijms25137006 PMid:39000116 PMCid:PMC11241432
9. Li H, Förstermann U. Uncoupling of endothelial NO synthase in atherosclerosis and vascular disease. Curr Opin Pharm. 2013;13(2):161-7. https://doi.org/10.1016/j.coph.2013.01.006 PMid:23395155
10. Bennett BJ, de Aguiar Vallim TQ, Wang Z, et al. Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. Cell Metab. 2013;17(1):49-60. https://doi.org/10.1016/j.cmet.2012.12.011 PMid:23312283 PMCid:PMC3771112
11. Ke Y, Li D, Zhao M, et al. Gut flora-dependent metabolite trimethylamine-N-oxide accelerates endothelial cell senescence and vascular aging through oxidative stress. Free Radic Biol Med. 2018;116:88-100. https://doi.org/10.1016/j.freeradbiomed.2018.01.007 PMid:29325896 PMCid:PMC7495434
12. Zhang C, He J, Huo Y, et al. Gut microbial metabolite trimethylamine N-oxide as a novel predictor for adverse cardiovascular events after PCI: A systematic review and dose-response meta-analysis. Nutr J. 2025;24:91. https://doi.org/10.1186/s12937-025-01159-9 PMid:40524200 PMCid:PMC12168366
13. Kumar J. Microbial metabolites and cardiovascular dysfunction: A new era of diagnostics and therapy. Cells. 2025;14(16):1237. https://doi.org/10.3390/cells14161237 PMid:40862716 PMCid:PMC12384896
14. Pluznick JL, Protzko RJ, Gevorgyan H, et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. Proc Natl Acad Sci U S A. 2013;110(11):4410-5. https://doi.org/10.1073/pnas.1215927110 PMid:23401498 PMCid:PMC3600440
15. Milazzo G, Mercatelli D, Di Muzio G, et al. Histone deacetylases (HDACs): Evolution, specificity, role in transcriptional complexes, and pharmacological actionability. Genes (Basel). 2020;11(5):556. https://doi.org/10.3390/genes11050556 PMid:32429325 PMCid:PMC7288346
16. Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids: Linking diet, the microbiome and immunity. Nat Rev Immunol. 2024;24:577-95. https://doi.org/10.1038/s41577-024-01014-8 PMid:38565643
17. Han B, Lv X, Liu G, et al. Gut microbiota-related bile acid metabolism-FXR/TGR5 axis impacts the response to anti-α4β7-integrin therapy in humanized mice with colitis. Gut Microbes. 15(1):2232143. https://doi.org/10.1080/19490976.2023.2232143 PMid:37431863 PMCid:PMC10337508
18. Sondermann NC, Faßbender S, Hartung F, et al. Functions of the aryl hydrocarbon receptor (AHR) beyond the canonical AHR/ARNT signaling pathway. Biochem Pharmacol. 2023;208:115371. https://doi.org/10.1016/j.bcp.2022.115371 PMid:36528068 PMCid:PMC9884176
19. Li J, Zhao F, Wang Y, et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017;5:14. https://doi.org/10.1186/s40168-016-0222-x PMid:28143587 PMCid:PMC5286796
20. Li MN, Han Q, Wang N, et al. 16S rRNA gene sequencing for bacterial identification and infectious disease diagnosis. Biochem Biophys Res Commun. 2024;739:150974. https://doi.org/10.1016/j.bbrc.2024.150974 PMid:39550863
21. Koren O, Spor A, Felin J, et al. Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc Natl Acad Sci U S A. 2011;108(Suppl 1):4592-8. https://doi.org/10.1073/pnas.1011383107 PMid:20937873 PMCid:PMC3063583
22. Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in *apoe*−/− mice. Circulation. 2016;133(24):2434-46. https://doi.org/10.1161/CIRCULATIONAHA.115.019645 PMid:27143680

23. Oniszczuk A, Oniszczuk T, Gancarz M, Szymańska J. Role of gut microbiota, probiotics and prebiotics in the cardiovascular diseases. Molecules. 2021;26(4):1172. https://doi.org/10.3390/molecules26041172 PMid:33671813 PMCid:PMC7926819
24. Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. The effects of the mediterranean diet on health and gut microbiota. Nutrients. 2023;15(9):2150. https://doi.org/10.3390/nu15092150 PMid:37432307 PMCid:PMC10180651
25. Espín JC, González-Sarrías A, Tomás-Barberán FA. The gut microbiota: A key factor in the therapeutic effects of (poly)phenols. Biochem Pharmacol. 2017;139:82-93. https://doi.org/10.1016/j.bcp.2017.04.033 PMid:28483461
26. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19(5):576-85. https://doi.org/10.1038/nm.3145 PMid:23563705 PMCid:PMC3650111
27. Godos J, Guglielmetti M, Ferraris C, et al. Mediterranean diet and quality of life in adults: A systematic review. Nutrients. 2025;17(3):577. https://doi.org/10.3390/nu17030577 PMid:39940436 PMCid:PMC11819740
28. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure. Hypertension. 2014;64(4):897-903. https://doi.org/10.1161/HYPERTENSIONAHA.114.03469 PMid:25047574 PMCid:PMC10602761
29. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutr Res Rev. 2018;31(1):35-51. https://doi.org/10.1017/S095442241700018X PMid:29037268
30. Armani RG, Carvalho AB, Ramos CI, et al. Effect of fructooligosaccharide on endothelial function in CKD patients: A randomized controlled trial. Nephrol Dial Transplant. 2021;37(1):85-91. https://doi.org/10.1093/ndt/gfaa335 PMid:33411910
31. Vrieze A, Nood EV, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143(4):913-6.e7. https://doi.org/10.1053/j.gastro.2012.06.031 PMid:22728514
32. Szajewska H, Scott KP, de Meij T, et al. Antibiotic-perturbed microbiota and the role of probiotics. Nat Rev Gastroenterol Hepatol. 2025;22(3):155-72. https://doi.org/10.1038/s41575-024-01023-x PMid:39663462
33. Dongre DS, Saha UB, Saroj SD. Exploring the role of gut microbiota in antibiotic resistance and prevention. Ann Med. 2025;57(1):2478317. https://doi.org/10.1080/07853890.2025.2478317 PMid:40096354 PMCid:PMC11915737
34. PubChem. PubChem compound summary for CID 12233, 3,3-dimethyl-1-butanol. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/3_3-Dimethyl-1-butanol (Accessed: 20 March 2026).
35. Wang Z, Roberts AB, Buffa JA, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. Cell. 2015;163(7):1585-95. https://doi.org/10.1016/j.cell.2015.11.055 PMid:26687352 PMCid:PMC4871610
36. Yu J, Wu Y, Zhu Z, et al. The impact of dietary patterns on gut microbiota for the primary and secondary prevention of cardiovascular disease: A systematic review. Nutr J. 2025;24:17. https://doi.org/10.1186/s12937-024-01060-x PMid:39875854 PMCid:PMC11773984
37. Nwabudike LC, Elisei AM, Buzia OD, Miulescu M, Tatu AL. Statins. A review on structural perspectives, adverse reactions and relations with non-melanoma skin cancer. Rev Chim. 2018;69(9):2557-62. https://doi.org/10.37358/RC.18.9.6575
38. Hu X, Li H, Zhao X, et al. Multi-omics study reveals that statin therapy is associated with restoration of gut microbiota homeostasis and improvement in outcomes in patients with acute coronary syndrome. Theranostics. 2021;11(12):5778-93. https://doi.org/10.7150/thno.55946 PMid:33897881 PMCid:PMC8058718
39. Kim J, Lee H, An J, et al. Alterations in gut microbiota by statin therapy and possible intermediate effects on hyperglycemia and hyperlipidemia. Front Microbiol. 2019;10:1947. https://doi.org/10.3389/fmicb.2019.01947 PMid:31551944 PMCid:PMC6736992
40. Tatu AL, Ciobotaru OR, Miulescu M, et al. Hydrochlorothiazide: Chemical structure, therapeutic, phototoxic and carcinogenetic effects in dermatology. Rev Chim. 2018;69(8):2110-4. https://doi.org/10.37358/RC.18.8.6484
41. Paraskevaidis I, Briasoulis A, Tsougos E. Oral cardiac drug-gut microbiota interaction in chronic heart failure patients: An emerging association. Int J Mol Sci. 2024;25(3):1716. https://doi.org/10.3390/ijms25031716 PMid:38338995 PMCid:PMC10855150
42. González-Correa C, Miñano S, Moleón J, et al. The probiotic *limosilactobacillus fermentum* CECT5716 enhances the antihypertensive response to hydrochlorothiazide in spontaneously hypertensive rats. Gut Microbes. 17(1):2586324. https://doi.org/10.1080/19490976.2025.2586324 PMid:41254951 PMCid:PMC12645898