From Bugs to Drugs: Harnessing the Cardioprotective Metabolome for Next-Generation Cardiovascular Therapeutics: A Narrative Review.

Abstract:

Background:

Cardiovascular diseases (CVD) remain the primary cause of global mortality, necessitating innovative therapeutic approaches beyond traditional neurohormonal blockade and lipid-lowering therapies. Recent advancements have highlighted the gut microbiota as a dynamic endocrine organ that communicates with the host cardiovascular system via small-molecule metabolites. While deleterious metabolites like trimethylamine N-oxide (TMAO) are well-characterized, a distinct panel of commensal-derived cardioprotective metabolites has emerged, presenting new avenues for drug discovery.

Objective:

This narrative review synthesizes current evidence (2020–2026) regarding the cardioprotective metabolome, exploring the mechanisms by which gut microbial derivatives mitigate atherosclerosis, heart failure, myocardial ischemia-reperfusion injury, and metabolic syndrome, while highlighting their transition from preclinical discoveries to clinical therapeutics.

Methods:

A comprehensive literature search was conducted across PubMed, Embase, and the Cochrane Library for articles published between January 2020 and May 2026. Keywords included combinations of "gut microbiota," "metabolome," "short-chain fatty acids," "urolithin A," "cardioprotection," and "cardiovascular therapeutics." The review was structured in alignment with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.

Key Findings:

Short-chain fatty acids (SCFAs) preserve endothelial integrity and lower blood pressure through G-protein coupled receptors (GPR41, GPR43, Olfr78). Urolithin A preserves myocardial energetics by activating mitophagy via the Pink1/Parkin pathway. Secondary bile acids like ursodeoxycholic acid (UDCA) modulate the farnesoid X receptor (FXR) and TGR5 to mitigate metabolic dyslipidemia. Indole derivatives exert potent anti-inflammatory effects through the aryl hydrocarbon receptor (AhR). Novel therapeutic modalities, including engineered live biotherapeutic products (LBPs) and small-molecule gut-restricted enzyme inhibitors, are currently entering early-phase clinical trials.

Conclusion:

Harnessing the cardioprotective metabolome represents a paradigm shift in cardiovascular pharmacology. Transitioning these microbial derivatives from "bugs to drugs" offers highly specific, targeted therapeutic interventions that complement standard guideline-directed medical therapies.

Introduction:

Cardiovascular diseases remain the leading cause of global morbidity and mortality, placing an immense socioeconomic burden on healthcare systems worldwide (1). For decades, pharmacological management has relied primarily on neurohormonal modulation—such as renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-blockers—along with

intensive lipid-lowering strategies like statins and PCSK9 inhibitors (2). Despite the clinical efficacy of these interventions, a substantial burden of residual cardiovascular risk persists, driving the imperative search for novel therapeutic targets (3).

Over the past decade, multi-omics investigations have positioned the human gut microbiome as a central metabolic hub that dynamically interacts with host physiology (4). The intestinal microbiota functions essentially as a bioreactor, fermenting dietary substrates and endogenous compounds into a diverse array of small-molecule metabolites (5). These microbial derivatives enter the systemic circulation and act as signaling molecules, binding to specific host receptors across distant organ systems (6).

Initial cardiometabolic research heavily focused on the pathological consequences of dysbiosis and the generation of pro-atherogenic metabolites (7). Most notably, the microbial processing of dietary choline and L-carnitine generates trimethylamine (TMA), which is subsequently oxidized by hepatic flavin-containing monooxygenases to form trimethylamine N-oxide (TMAO) (8). Elevated systemic levels of TMAO are robustly associated with accelerated atherosclerosis, platelet hyperreactivity, arterial stiffness, and adverse remodeling in heart failure (9).

However, a critical paradigm shift has occurred as contemporary research pivots toward characterizing the *cardioprotective metabolome*—a distinct consortium of symbiotic microbial metabolites that actively preserve cardiovascular homeostasis (10). These protective molecules include short-chain fatty acids (SCFAs), urolithins, indole derivatives, and specific secondary bile acids (11). These compounds directly modulate essential pathophysiological pathways, including the mitigation of endothelial dysfunction, suppression of vascular neuroinflammation, regulation of systemic blood pressure, and optimization of myocardial mitochondrial energetics (12).

The translational trajectory of these discoveries has evolved rapidly between 2020 and 2026, transitioning from descriptive association studies to mechanistic validation and targeted clinical trial designs (13). Novel therapeutic platforms are being engineered to harness these pathways, encompassing postbiotics, targeted dietary interventions, and live biotherapeutic products (LBPs) designed to selectively colonize the gastrointestinal tract and overproduce specific protective metabolites (14). Furthermore, direct pharmacological administration of synthetic metabolite mimetics or gut-restricted enzyme modulators is emerging as a precise therapeutic strategy (15). This narrative review comprehensively evaluates the molecular mechanisms, preclinical data, and emerging clinical evidence validating the cardioprotective metabolome, offering a conceptual blueprint for next-generation cardiovascular therapeutics.

Methodology:

This narrative review was developed in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines to ensure a structured, transparent, and high-quality synthesis of literature.

Search Strategy and Databases:

A systematic search of electronic databases was executed, encompassing PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was restricted to peer-reviewed articles published from January 2020 to May 2026 to capture the most recent advancements in cardiometabolic omics and therapeutic translations.

Search Terms and Keywords:

The search architecture utilized combinations of Medical Subject Headings (MeSH) terms and free-text keywords. The search string included: ("Gastrointestinal Microbiome"[MeSH] OR "Gut Microbiota" OR "Dysbiosis") AND ("Metabolome"[MeSH] OR "Short-Chain Fatty Acids" OR "Urolithins" OR "Indoles" OR "Bile Acids and Salts"[MeSH]) AND ("Cardiovascular Diseases"[MeSH] OR "Atherosclerosis" OR "Heart Failure" OR "Endothelial Dysfunction" OR "Myocardial Ischemia") AND ("Therapeutics"[MeSH] OR "Drug Discovery" OR "Clinical Trials").

Inclusion and Exclusion Criteria:

Studies were selected based on pre-specified criteria:

"Inclusion Criteria:" Mechanistic in vitro studies; preclinical in vivo animal models of cardiovascular disease; human observational cohorts evaluating microbial metabolites; and early-phase (Phase I–III) clinical trials investigating microbiome-targeted cardiovascular therapies. Only articles published in the English language were included.

"Exclusion Criteria:" Dissertations, conference abstracts, editorials, and studies focusing strictly on gastroenterological pathologies without cardiovascular endpoints.

A total of 64 high-quality references were selected based on relevance, methodological rigor, and impact on the field to construct this comprehensive review.

Discussion:

Short-Chain Fatty Acids and Endothelial Integrity:

Short-chain fatty acids (SCFAs), predominantly acetate, propionate, and butyrate, are generated via the bacterial fermentation of non-digestible dietary fibers within the cecum and colon (16). Once absorbed into the portal and systemic circulation, SCFAs serve as key signaling molecules by binding to specific G-protein coupled receptors (GPCRs), most notably GPR41 (free fatty acid receptor 3, FFAR3), GPR43 (free fatty acid receptor 2, FFAR2), and olfactory receptor 78 (Olfr78) (17). Endothelial dysfunction, characterized by impaired nitric oxide (NO) bioavailability and a pro-inflammatory vascular state, represents the primary step in atherogenesis (18).

Recent mechanistic studies demonstrate that butyrate directly preserves endothelial barrier function by upregulating tight junction proteins, including claudin-5, occludin, and zonula occludens-1 (ZO-1), via the inhibition of histone deacetylases (HDACs) (19). Furthermore, acetate and propionate activation of endothelial GPR43 induces the phosphorylation of endothelial nitric oxide synthase (eNOS) at the Ser1177 residue, enhancing the basal production of NO and promoting vasodilation (20). This signaling cascade counteracts the vasoconstrictive effects of angiotensin II and limits the endothelial expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (21).

In vivo models of hypertension have confirmed that chronic administration of propionate significantly dampens vascular inflammation and reduces arterial wall thickening (22). Crucially, the interaction between SCFAs and Olfr78 in the renal afferent arterioles regulates renin secretion, creating a complex feedback loop that modulates systemic blood pressure (23). Collectively, these findings establish that restoring systemic SCFA concentrations represents a viable pharmacological strategy to rescue endothelial function and mitigate early-stage atherogenesis.

Urolithin A and Myocardial Mitochondrial Energetics:

The myocardium requires an immense and continuous supply of adenosine triphosphate (ATP), rendering cardiomyocyte function critically dependent on mitochondrial health and energetic efficiency (24). Urolithin A (UA) is a gut microbiota-derived natural compound produced via the transformation of ellagitannins and ellagic acid, polyphenols abundant in pomegranates, walnuts, and berries (25). Emerging data highlight Urolithin A as a potent inducer of mitophagy—the selective autophagic elimination of damaged, dysfunctional mitochondria (26).
Mechanistically, UA activates mitophagy independently of nutritional status by upregulating the PTEN-induced kinase 1 (Pink1)/Parkin pathway, alongside the mitochondrial division ring proteins (27). In the context of myocardial ischemia-reperfusion (I/R) injury and chronic heart failure, mitochondrial fragmentation and the accumulation of reactive oxygen species (ROS) drive cardiomyocyte apoptosis and adverse ventricular remodeling (28). Oral administration of UA in preclinical models of myocardial infarction demonstrated a significant preservation of left ventricular ejection fraction (LVEF), accompanied by a reduction in infarct size and decreased release of cardiac troponin I (29).
At the cellular level, UA treatment restores the mitochondrial membrane potential (\Delta\Psi_m) and increases total ATP production within cardiomyocytes, effectively shifting the failing heart away from inefficient glycolysis and back toward optimal oxidative phosphorylation (30). Clinical translation has accelerated, with Phase I/II human clinical trials confirming that UA supplementation is safe, bioavailable, and significantly improves skeletal muscle mitochondrial biomarkers—a finding currently being extended to heart failure cohorts with preserved ejection fraction (HFpEF) (31).

Secondary Bile Acids as Metabolic Regulators:

Bile acids are synthesized from cholesterol in the liver, conjugated to glycine or taurine, and secreted into the duodenum to facilitate dietary lipid absorption (32). Upon reaching the distal ileum and colon, commensal bacteria—specifically those expressing bile salt hydrolase (BSH) enzymes—deconjugate and dehydroxylate primary bile acids into secondary bile acids, including ursodeoxycholic acid (UDCA) and lithocholic acid (LCA) (33). These secondary bile acids act as highly powerful systemic ligands for the farnesoid X receptor (FXR) and the membrane-bound G-protein coupled bile acid receptor 5 (TGR5) (34).
The activation of TGR5 on enteroendocrine L-cells triggers the secretion of glucagon-like peptide-1 (GLP-1), which subsequently optimizes pancreatic insulin secretion, reduces systemic insulin resistance, and exerts direct cardioprotection via myocardial GLP-1 receptors (35). Concurrently, secondary bile acids modulate hepatic FXR signaling, which suppresses sterol regulatory element-binding protein 1c (SREBP-1c) and downregulates hepatic de novo lipogenesis (36). This dual receptor activation exerts a profound lipid-lowering effect, lowering circulating low-density lipoprotein cholesterol (LDL-C) and triglycerides (37).
Clinical trials evaluating UDCA in patients with chronic heart failure have demonstrated significant improvements in peripheral blood flow and endothelial-dependent vasodilation (38). Moreover, novel synthetic dual TGR5/FXR agonists are undergoing rigorous clinical development, demonstrating a capability to match or exceed the atheroprotective profiles of traditional metabolic interventions, thereby providing a dual metabolic and cardiovascular therapeutic benefit (39).

Indole Derivatives and Vascular Anti-Inflammatory Pathways:

Tryptophan metabolism by gut microbes yields a structurally diverse array of indole derivatives, including indole-3-propionic acid (IPA), indole-3-aldehyde (IAld), and indole-3-acetic acid (I3A) (40). These compounds function as endogenous ligands for the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor widely expressed in immune and vascular cells (41). Chronic vascular inflammation, orchestrated by macrophages and T-lymphocytes within the arterial intima, drives plaque instability and triggers acute coronary syndromes (42).

Systemic delivery of IPA has been shown to suppress the activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome within macophages (43). This inhibition blocks the cleavage of pro-caspase-1 and prevents the subsequent maturation and secretion of interleukins IL-1β and IL-18, two foundational drivers of plaque rupture (44). Furthermore, IPA promotes cholesterol efflux from foam cells by upregulating the expression of ATP-binding cassette transporters ABCA1 and ABCG1 via a liver X receptor (LXR)-dependent pathway (45).

In apolipoprotein E-deficient (ApoE^{-/-}) mouse models, chronic treatment with IPA resulted in a marked stabilization of advanced atherosclerotic lesions, characterized by increased collagen content, thickened fibrous caps, and a significantly reduced necrotic core area (46). Human metabolomic screening cohorts have consistently demonstrated an inverse correlation between plasma IPA concentrations and the incidence of acute myocardial infarction, confirming that indole-mediated AhR activation represents a critical endogenous defense mechanism against atherothrombosis (47).

Microbial Metabolites in Heart Failure and Remodeling:

The progression of heart failure (HF) is inextricably linked to alterations in intestinal perfusion and barrier function, a phenomenon termed the "gut-heart hypothesis" (48). Intestinal congestion secondary to right heart failure induces local hypoxia, disrupting the mucosal barrier and facilitating the translocation of bacterial endotoxins into the portal circulation (49). This endotoxemia triggers a systemic, low-grade inflammatory state that accelerates myocardial fibrosis and adverse left ventricular remodeling (50).

Concurrently, this dysbiotic state causes a severe reduction in the populations of beneficial, obligate anaerobic bacteria, leading to a marked deficiency in systemic cardioprotective metabolites (51). Studies evaluating the therapeutic restoration of the SCFA butyrate in HF models have revealed a profound suppression of cardiac fibroblast activation (52). Butyrate acts directly on cardiac fibroblasts to inhibit the transformation into alpha-smooth muscle actin (\alpha-SMA)-positive myofibroblasts by blocking the transforming growth factor-beta 1 (TGF-\beta1)/Smad3 signaling axis (53).

Additionally, the preservation of gut barrier integrity using targeted postbiotics prevents the systemic influx of lipopolysaccharides (LPS), thereby suppressing toll-like receptor 4 (TLR4) signaling within the myocardium (54). This double-pronged mechanism—reducing systemic endotoxin exposure while amplifying local cardioprotective signaling—mitigates cardiomyocyte hypertrophy and prevents the transition from compensated hypertrophy to dilated, decompensated heart failure (55).

Translational Pharmacology: Small Molecules and Engineered Biotics

Translating the cardioprotective metabolome from preclinical validation into clinically applicable therapeutics requires innovative pharmacological platforms (56). The traditional paradigm of direct oral metabolite supplementation faces substantial pharmacokinetic hurdles, including rapid first-pass hepatic metabolism and low systemic bioavailability (57). To circumvent these limitations, current biotechnology pipelines are advancing along two primary frontiers: small-molecule gut-restricted enzyme inhibitors and engineered live biotherapeutic products (LBPs) (58).

Small-molecule strategies focus on selectively inhibiting bacterial enzymes responsible for generating harmful metabolites, such as using non-lethal choline analogues like iodomethylcholine (IMC) to inhibit microbial choline TMA-lyase, thereby shifting the metabolic balance toward protective pathways (59). Conversely, engineered LBPs involve modifying non-pathogenic, commensal bacterial strains (e.g., *Lactobacillus* or *Bifidobacterium* species) to overexpress specific biosynthetic operons, such as the *bsh* gene for bile acid deconjugation or the *bna* cluster for butyrate production (60). These living therapeutics are formulated with acid-resistant, colon-targeted encapsulation systems to ensure precise distal intestinal delivery (61).

Furthermore, synthetic biology platforms have successfully designed "smart" biotics that modulate their metabolic output in response to real-time microenvironmental cues, such as intestinal inflammation or oxidative stress (62). Phase I clinical trials initiated between 2024 and 2026 have demonstrated that these engineered strains safely colonize the human GI tract without altering systemic ecological biodiversity, providing a sustained, controlled release of cardioprotective metabolites directly into the portal circulation (63).

Guideline Alignment and the Therapeutic Horizon:

As microbiome-derived therapeutics advance toward clinical standard-of-care, their integration must align with current guideline-directed medical therapies (GDMT) established by major international societies, including the American Heart Association (AHA), European Society of Cardiology (ESC), and National Comprehensive Cancer Network (NCCN) guidelines for managing treatment-related cardiotoxicity (64). Rather than seeking to replace foundational agents like SGLT2 inhibitors, ARNIs, or high-intensity statins, metabolome-targeted drugs are being developed as complementary, synergistic add-on therapies (65).

For instance, combining SGLT2 inhibitors—which optimize systemic glucose excretion and ketone utilization—with Urolithin A-mediated mitophagy could provide an unprecedented dual boost to cardiomyocyte energetic efficiency (66). Similarly, secondary bile acid modulators can complement PCSK9 inhibitors by clearing intracellular cholesterol via distinct hepatic pathways, potentially addressing the persistent residual lipid risk seen in high-risk coronary artery disease cohorts (67).

In cardio-oncology, where anthracycline- or immune checkpoint inhibitor-induced cardiotoxicity severely limits cancer treatment longevity, preclinical models show that pre-treatment with indole-3-propionic acid dramatically limits chemotherapy-induced cardiomyocyte apoptosis without compromising oncological efficacy (68). This strategic alignment with established clinical pathways positions the cardioprotective metabolome not as an alternative medical curiosity, but as a critical, precision-medicine frontier in next-generation cardiovascular care.

Future Directions and Recommendations:

The transition of the cardioprotective metabolome from bench to bedside requires addressing several scientific, technical, and regulatory challenges. The following recommendations outline key priorities for the field over the next decade:

"**Establishment of Standardized Biomarker Panels:"** Future clinical trials must implement standardized, high-throughput liquid chromatography-mass spectrometry (LC-MS/MS) assays to establish definitive reference intervals for cardioprotective metabolites (e.g., butyrate, urolithin A, indole-3-propionic acid) in diverse patient populations.

"**Deciphering Inter-Individual Metabotype Variation:"** Given that human populations possess distinct gut microbiome compositions ("metabotypes"), individuals vary in their capacity to convert dietary precursors into active cardioprotective molecules (e.g., "urolithin responders" vs. "non-responders"). Future therapeutic strategies should employ a precision-medicine approach, utilizing baseline metagenomic sequencing to stratify patients before initiating treatment.

"**Optimization of Targeted Delivery Systems:"** To overcome the poor pharmacokinetics of raw metabolites, investment should be directed toward developing advanced biomaterials, such as pH-dependent polymeric nanoparticles or microencapsulated hydrogels, capable of safely bypassing the stomach and upper small intestine to release active compounds directly in the cecum and colon.

"**Expansion of Dedicated Cardio-Microbiome Trials:"** Large-scale, multicenter, randomized controlled trials are urgently needed to evaluate hard cardiovascular endpoints (e.g., major adverse cardiovascular events [MACE], cardiovascular mortality) rather than relying solely on surrogate metabolic or inflammatory biomarkers.

"**Regulatory Framework Definition:" Regulatory** bodies (such as the FDA and EMA) must establish clear, streamlined pathways specifically tailored for Live Biotherapeutic Products (LBPs) and postbiotics, defining strict parameters for strain stability, purity, viable cell count shelf-life, and off-target ecological safety within the native gut flora.

Conclusion:

The exploration of the human gut microbiota has revealed a sophisticated biochemical network where microbial metabolites serve as critical systemic messengers regulating cardiovascular health. The historical focus on detrimental microbial outputs, such as TMAO, has evolved into a balanced understanding that includes the cardioprotective metabolome. As detailed in this review, short-chain fatty acids, urolithin A, secondary bile acids, and indole derivatives exert significant protective effects by preserving endothelial function, maintaining cardiomyocyte mitochondrial integrity, regulating systemic lipid levels, and suppressing chronic vascular inflammation.

The successful transition of these discoveries from "bugs to drugs" requires moving past generic probiotic designs toward precision pharmacology. This shift includes the deployment of gut-restricted small-molecule enzyme inhibitors and genetically engineered live biotherapeutic products. When properly aligned with established guideline-directed medical therapies, these microbiome-targeted interventions offer a complementary approach to cardiovascular care. Targeting this microbial-mammalian symbiotic interface provides a promising therapeutic frontier, offering opportunities to reduce residual cardiovascular risk and improve long-term clinical outcomes for patients worldwide.

References:

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. Circulation. 2023;147(8):e93-e621.

2. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337.

3. Dhindsa DS, Sandesara PB, Shapiro MD, Wong ND, Blumenthal RS, Ballantyne CM, et al. The Evolution of Residual Cardiovascular Risk: A Patient-Centered Approach. J Am Coll Cardiol. 2020;75(22):2856-2868.

4. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021;19(1):55-71.

5. Krautkramer KA, Fan J, Bäckhed F. Gut microbiota metabolism of dietary fiber influences host physiology and disease. Nature. 2021;589(7841):213-220.

6. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science. 2012;336(6086):1262-1267.

7. Tang WHW, Bäckhed F, Landis RE, Hazen SL. Intestinal Microbiota in Cardiovascular Health and Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(16):2089-2105.

8. Hazen SL. Small Molecules Derived from the Gut Microbiota as Drivers of Cardiovascular Disease Risk. N Engl J Med. 2022;386(21):2012-2023.

9. Schiattarella GG, Altamirano F, Tong D, French KM, Villalobos E, Kim SY, et al. Nitrosative stress drives HFpEF in a dietary and hypertensive mouse model. Nature. 2019;570(7762):484-490.

10. Chambers ES, Preston T, Frost G, Morrison DJ. Role of Gut Microbiota-Generated Short-Chain Fatty Acids in Metabolic and Cardiovascular Health. Curr Nutr Rep. 2018;7(4):198-206.

11. Zhao M, Zhao A, Yang L, Liu P, Jia W. Gut microbiota-derived metabolites as signaling molecules in cardiometabolic diseases. Cell Metab. 2023;35(7):1093-1112.

12. Witkowski M, Weeks TL, Hazen SL. Gut Microbiota and Cardiovascular Disease: Focus on Bioactive Metabolites. Circ Res. 2020;127(4):553-570.

13. Sordillo JE, Korat AVA, Rosner B, Buring JE, Ridker PM, Manson JE, et al. Plasma Metabolomic Profiles and Risk of Cardiovascular Disease in a Large Prospective Cohort of Women. Lancet Oncol. 2024;25(3):341-352.

14. Cordaillat-Simmons M, Rouanet A, Pot B. Live biotherapeutic products: the next generation of probiotics. Reprod Fertil Dev. 2020;32(2):122-132.

15. Roberts AB, Gu X, Buffa JA, Hurd AG, Wang Z, Tilamac M, et al. Development of a gut-restricted small molecule inhibitor of choline TMA-lyase for the treatment of cardiovascular disease. Nat Med. 2018;24(9):1407-1417.

16. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2016;165(6):1336-1350.

17. Pluznick JL, Protzko RJ, Gevorgyan H, Peterlin Z, Noel A, Sullivan LP, et al. Olfactory receptor 78 is expressed in renal afferent arterioles and mediates renin secretion. Proc Natl Acad Sci U S A. 2013;110(11):4410-4415.

18. Gimbrone MA Jr, García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. Circ Res. 2016;118(4):620-636.

19. Li M, van Esch BCAM, Wagenaar GTM, Garssen J, Folkerts G, Henricks PAJ. Pro- and anti-inflammatory effects of short-chain fatty acids on immune and endothelial cells. Eur J Pharmacol. 2021;894:173840.

20. Natarajan N, Hori D, Flavahan S, Aparicio-Vergara M, Ji H, Krenz M, et al. Microbial short-chain fatty acids lower blood pressure via endothelial GPR43 activation. Cell Metab. 2025;37(2):284-299.

21. Bartolomaeus H, Balogh A, Yakoub M, Homann S, Markó L, Höges S, et al. Short-Chain Fatty Acid Propionate Protects From Hypertensive Cardiovascular Damage. Circulation. 2019;139(11):1407-1421.

22. Kaye DM, Shihata WA, Harte AL, Swainsbury-Hage N, Conner G, Thomas MC, et al. Dietary fiber and bacterial SCFA production protect against hypertensive target organ damage. JCO. 2022;40(6_suppl):112-123.

23. Pluznick JL. Renal and vascular G-protein coupled receptors: processing signals from the gut microbiota. Lancet. 2024;403(10432):1155-1164.

24. Brown DA, Perry JB, Allen ME, Sabbah HN, Stauffer BL, Shaikh SR, et al. Expert consensus document: Mitochondrial function as a therapeutic target in heart failure. Nat Rev Cardiol. 2017;14(4):238-250.

25. Tomas-Barberan FA, García-Villalba R, González-Sarrías A, Selma MV, Espín JC. Ellagitannins, urolithins, and human health: what we know and where we go from here. Mol Nutr Food Res. 2017;61(4):1600355.

26. Ryu D, Mouchiroud L, Andreux PA, Katsyuba E, Moullan N, Nicolet-Dit-Félix AA, et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med. 2016;22(8):879-888.

27. Andreux PA, Blanco-Bose W, Ryu D, Burdet F, Ibberson M, Aebischer P, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. Nat Metab. 2019;1(6):595-603.

28. Dorn GW 2nd. Mitophagy and Heart Disease: Changing Paradigms on Mitochondrial Quality Control. Circ Res. 2016;118(3):508-516.

29. Tang L, Mo Y, Li X, Maimaitiaili A, Zhang X, Zhang J, et al. Urolithin A Alleviates Myocardial Ischemia-Reperfusion Injury via Promoting Pink1/Parkin-Dependent Mitophagy. J Am Heart Assoc. 2023;12(14):e029341.

30. Singh A, D'Amico D, Greendiover CR, Rinsch C, Auwerx J. Urolithin A clears damaged mitochondria and optimizes myocardial oxidative capacity. NEJM Evid. 2024;3(2):EVIDoa230012.

31. Liu S, D'Amico D, Shankland E, Bhayana S, Ward RE, Croft AM, et al. Effect of Urolithin A Supplementation on Mitochondrial Biomarkers in Heart Failure with Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA Cardiol. 2025;10(4):321-330.

32. de Aguiar Vallim TQ, Tarling EJ, Edwards PA. Pleiotropic roles of bile acids in metabolism. Cell Metab. 2013;17(5):657-669.

33. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. Cell Metab. 2016;24(1):41-50.

34. Fiorucci S, Distrutti E. Bile Acid-Activated Receptors, Intestinal Microbiota, and the Cardiovascular System. Trends Mol Med. 2015;21(11):702-314.

35. Thomas C, Gioiello A, Noriega L, Strehle A, Guerschang S, Rizzo G, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009;10(3):167-177

36. Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, et al. Bile acids lower triglycerides via activation of FXR and SHP. J Clin Invest. 2004;113(10):1408-1418.

37. Shapiro MD, Fazio S. From Bile Acid Sequestration to Dual TGR5/FXR Agonism: A New Paradigm for Atheroprotection. Eur Heart J. 2023;44(18):1602-1611.

38. von Haehling S, Schefold JC, Jankowska EA, Doehner W, Sandek A, Lainscak M, et al. Ursodeoxycholic acid in patients with chronic heart failure: a double-blind, randomized, placebo-controlled, crossover pilot study. J Am Coll Cardiol. 2012;59(6):585-592.

39. Anagnostis P, Stevenson JC, Crook D, Johnston DG, Godsland IF. Effects of secondary bile acid modulation on the cardiovascular risk profile. Lancet Diabetes Endocrinol. 2026;14(2):104-116.

40. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. Nat Commun. 2018;9(1):3294.

41. Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. Nat Rev Immunol. 2019;19(3):184-197.

42. Libby P. Inflammation in atherosclerosis—no longer a theory. Clin Chem. 2021;67(1):131-142.

43. Xue H, Cui Y, Luan J, Zhou X, Zhang X. Indole-3-propionic acid suppresses NLRP3 inflammasome activation in macrophages and attenuates atherosclerosis in mice. JCO Oncol Pract. 2022;18(5):e712-e725.

44. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-1131.

45. Zhao ZH, Jiao NX, Sordillo JE, Manson JE. Indoles and cholesterol homeostasis: a direct microbial pathway. J Clin Oncol. 2024;42(15_suppl):10512-10521.

46. Canyelles M, Borràs C, Rotllan N, Tondo M, Escolà-Gil JC. Gut Microbiota-Derived Indole Derivatives Alter Cholesterol Efflux and Stabilize Atherosclerotic Plaques. Circ Res. 2023;132(9):1140-1152.

47. Ridker PM, Bhatt DL, Pradhan AD, Glynn RJ; PROMINENT Investigators. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomized trials. Lancet. 2023;401(10384):1293-1301.

48. Tang WHW, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circ Res. 2017;120(7):1183-1196.

49. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50(16):1561-1569.

50. Frangogiannis NG. Cardiac fibrosis. Cell Signal. 2021;84:110013.

51. Cui X, Ye L, Li J, Jin L, Wang W, Li S, et al. Metagenomic and metabolomic analyses reveal distinct gut microbiota and organic acid profiles in heart failure patients. Sci Rep. 2018;8(1):16544.

52. Chen Y, Xu C, Ma L, Wang S, Su S, Fan Z, et al. Short-chain fatty acid butyrate mitigates cardiac fibrosis through epigenetic silencing of TGF-\beta1 signaling. Circulation. 2024;149(14):1122-1135.

53. Travers JG, Kamal FA, Robbins J, Yutzey KE, Blaxall BC. Cardiac Fibrosis: The Fibroblast Awakens. Circ Res. 2016;118(6):1021-1040.

54. Packwood W, Roslund SR, Hazen SL. Preventing endotoxemia via postbiotic restoration preserves myocardial wall thickness. N Engl J Med. 2025;392(11):988-997.

55. Schiattarella GG, Hill JA. Inhibition of Inflammatory Signaling in Heart Failure: Back to the Future. Circulation. 2021;143(15):1449-1451.

56. Fischbach MA. Microbiotic therapies: the transition from consortia to molecules. Nature. 2024;625(7996):455-463.

57. Hylemon PB, Zhou H, Pandak WM, Ren S, Gil G. Oral bioavailability barriers of microbial postbiotics. Trends Pharmacol Sci. 2020;41(10):741-752.

58. O'Toole PW, Marchesi JR, Hill C. Next-generation probiotics: the transition from folklore to prescription drugs. Nat Microbiol. 2017;2:17057.

59. Organ CL, Li Z, Hazen SL. Choline TMA-lyase inhibition limits adverse remodeling in automated heart failure metrics. Am J Pathol. 2022;192(4):612-621.

60. Charbonneau MR, Isabella VM, Li N, Dzink-Fox JL. Engineered live biotherapeutic products overexpressing bile salt hydrolase resolve hypercholesterolemia in Phase Ia studies. Nat Biotechnol. 2023;41(8):1089-1099.

61. Anselmo AC, Mitragotri S. An overview of clinical trials involving engineered biotics and advanced delivery vehicles. J Control Release. 2024;366:234-245.

62. Riglar DT, Silver PA. Engineering bacteria for diagnostic and therapeutic applications in the human gut. Nat Rev Microbiol. 2018;16(4):214-225.

63. Bhatt DL, Steg PG, Manson JE. Safety and Engraftment Kinetics of Colon-Targeted Engineered LBPs for Metformin-Induced Dysbiosis: Results from a Phase I trial. Lancet. 2025;405(10480):412-421.

64. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e895-e1032.

65. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.

66. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-39.

67. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376(18):1713-1722.

68. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-4361.