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Understanding The Role of Microbial Metabolites in Heart Failure Pathogenesis

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Abstract

The gut-heart axis represents a critical pathway linking gut microbiota to cardiovascular health. In heart failure (HF), gut dysbiosis and altered microbial metabolites are thought to contribute to systemic inflammation and metabolic disturbances that may accelerate disease progression. This narrative review summarizes current clinical and experimental evidence on gut dysbiosis and key microbial metabolites, and their mechanistic roles in HF pathogenesis. In patients with HF, microbial diversity is reduced, characterized by a depletion of anti-inflammatory taxa, and an overrepresentation of pro-inflammatory species. These compositional shifts also alter the concentration of microbial metabolites. For example, trimethylamine N-oxide level is elevated and associated with myocardial fibrosis and endothelial dysfunction, while short-chain fatty acids that exert anti-inflammatory effects and help preserve gut barrier integrity, are reduce. Other microbial metabolites also contribute to HF pathogenesis through distinct mechanism. Intestinal hypoperfusion in HF further increases gut permeability, facilitating the translocation of microbes and microbial metabolites, and triggering systemic inflammation. These alterations correlate with HF severity, prognosis, and clinical outcomes. Understanding the gut-heart axis, gut dysbiosis, and specific microbial metabolites may open new avenues for diagnosis and treatment in HF. Further research is needed to validate these mechanisms and assess the potential of microbiota-targeted therapies.

INTRODUCTION

Recent cardiovascular research has underscored the role of the gut microbiota's role in regulating systemic inflammation, metabolism, and immune responses. Central to this is the concept of the gut–heart axis, a bidirectional link between gut microbial activity and cardiovascular health (Jaimez-Alvarado et al., 2025; Rivera et al., 2024; Trøseid et al., 2020). Gut dysbiosis can impair intestinal barrier integrity, allowing microbial components like lipopolysaccharide (LPS) to enter the circulation, trigger systemic inflammation, and worsen cardiac outcomes (Jaimez-Alvarado et al., 2025).

Several gut-derived metabolites contribute to cardiovascular disease. Trimethylamine N-oxide (TMAO), for instance, promotes endothelial dysfunction, platelet activation, and atherosclerosis, and is linked to increased risks of heart failure (HF) and adverse cardiovascular events (Witkowski et al., 2020). In contrast, short-chain fatty acids (SCFAs) exert anti-inflammatory effects, support the gut barrier function, and support blood pressure regulation (Rivera et al., 2024; Trøseid et al., 2020).

Among cardiovascular disorders, HF is especially influenced by gut dysfunction. Reduced cardiac output in HF compromises intestinal perfusion, leading to mucosal ischemia, wall thickening, and impaired motility (Hao et al., 2024). These changes increase gut

permeability and raise circulating levels of zonulin, d-lactate, and lipopolysaccharide (LPS) (Perticone et al., 2024; Xiao et al., 2024). This barrier breakdown contributes to endotoxaemia, systemic inflammation, and worse clinical outcomes (Fountoulakis et al., 2025).

Concurrently, gut microbial profiles in HF patients show reduced diversity, depletion of SCFA-producing taxa like Ruminococcaceae, Lachnospiraceae, and Faecalibacterium, and enrichment of pro-inflammatory species such as Proteobacteria, Klebsiella, and Enterococcus (Cienkowski et al., 2024; Sun, 2025). These shifts correlate with increased levels of harmful metabolites like TMAO and phenylacetylglutamine (PAGln), which enhance platelet reactivity and thrombotic risk (Nemet et al., 2020).

Mechanistically, impaired perfusion in HF induces hypoxia, disrupts tight junction proteins, and promotes microbial translocation, fueling a cycle of chronic inflammation and cardiac decline (Drapała et al., 2020; Lupu et al., 2023). Both animal and human studies support this cascade, highlighting gut-derived mediators as drivers of HF progression (Fountoulakis et al., 2025).

The novelty of the present review lies in its comprehensive synthesis of recent evidence delineating the distinct mechanistic pathways of multiple key microbial metabolites--including SCFAs, TMAO, bile acids, indole-3-propionic acid (IPA), LPS, and IL-22--within the unified framework of HF pathogenesis, while also integrating recent insights from Mendelian randomization studies that suggest causal roles for specific gut microbes. Mechanistically, impaired perfusion in HF induces hypoxia, disrupts tight junction proteins, and promotes microbial translocation, fueling a cycle of chronic inflammation and cardiac decline. Both animal and human studies support this cascade, highlighting gut-derived mediators as drivers of HF progression.

Despite growing evidence, clinical applications remain limited. A deeper understanding of the gut microbiota, its metabolites, and their mechanistic role in HF is crucial to identifying new biomarkers and therapeutic targets. This review synthesizes current insights into the gut-heart axis, with a focus on the role of microbial metabolites in heart failure pathogenesis.

METHOD

This study employed a narrative literature review design to examine the role of microbial metabolites in the pathogenesis of heart failure (HF). The review aimed to synthesize current evidence regarding the interactions between gut microbiota, microbial-derived metabolites, and cardiovascular dysfunction through the gut–heart axis. Relevant literature was identified through electronic databases, including PubMed, Scopus, ScienceDirect, and Google Scholar. The literature search focused on articles published between 2020 and 2025 using the keywords: *heart failure*, *gut microbiota*, *gut dysbiosis*, *microbial metabolites*, *gut–heart axis*, *trimethylamine N-oxide (TMAO)*, *short-chain fatty acids (SCFAs)*, *bile acids*, *indole-3-propionic acid (IPA)*, and *lipopolysaccharide (LPS)*.

The inclusion criteria comprised original research articles, systematic reviews, meta-analyses, and narrative reviews published in English that discussed the mechanisms, clinical implications, and therapeutic potential of microbial metabolites in heart failure. Studies unrelated to cardiovascular diseases, non-peer-reviewed publications, conference abstracts, and duplicate articles were excluded. The selected literature was critically reviewed and analyzed to identify key findings regarding gut microbial alterations, metabolite production,

inflammatory pathways, and their contributions to cardiac remodelling and disease progression.

Data extracted from the included studies were synthesized descriptively and organized according to major themes, including intestinal barrier dysfunction, gut dysbiosis, microbial metabolites involved in heart failure pathogenesis, and microbiota-targeted therapeutic interventions. The findings were then presented narratively to provide a comprehensive understanding of the current evidence concerning the role of microbial metabolites in heart failure and their potential application as diagnostic biomarkers and therapeutic targets.

RESULT AND DISCUSSION

Gut-Heart Axis in Heart Failure Pathogenesis

Intestinal Barrier Dysfunction in Heart Failure

Heart failure (HF) causes hemodynamic changes that extend beyond the heart, notably impairing gastrointestinal function. A key consequence of reduced cardiac output is compromised intestinal perfusion, which disrupts the gut barrier and facilitates bacterial translocation, a phenomenon often termed "leaky gut". This process is now recognized as a major contributor to chronic systemic inflammation and adverse outcomes in HF (Drapała et al., 2020).

Reduced splanchnic blood flow leads to intestinal hypoxia, congestion, and mucosal injury. These conditions lead to downregulation of tight junction proteins such as occludin and ZO-1, which are essential for maintaining epithelial integrity (Drapała et al., 2020; Lupu et al., 2023; Paolillo et al., 2020). The resulting barrier disruption allows microbial components such as lipopolysaccharide (LPS) to enter the circulation, activating immune responses and sustaining chronic inflammation (Fountoulakis et al., 2025).

This pathophysiology has been demonstrated in both animal and human studies. Experimental HF models show rapid barrier breakdown and increased circulating LPS after reduced cardiac output (Paolillo et al., 2020). Similarly, patients with HF often present with elevated markers of gut permeability, including zonulin and d-lactate, along with signs of endotoxemia (Lupu et al., 2023; Perticone et al., 2024).

Gut Microbiota Alterations and Metabolic Implications in HF

In addition to structural barrier damage, HF is marked by gut microbiota dysbiosis, characterized by reduced beneficial taxa and increased pro-inflammatory microbes. These changes affect host metabolism and contribute to inflammation and cardiovascular dysfunction (Cienkowski et al., 2024).

Multiple studies report depletion of SCFA-producing bacteria in HF, such as Lachnospiraceae, Ruminococcaceae, Muribaculaceae, and Lactobacillaceae (Cienkowski et al., 2024). The loss of Prevotella spp., a key Bacteroidetes genus, also limits SCFA availability, impairing gut barrier integrity and immune regulation (Cienkowski et al., 2024).

Conversely, HF patients often show an overgrowth of potentially pathogenic taxa, including Proteobacteria and Actinobacteria (e.g., Escherichia, Shigella, Klebsiella) (Cienkowski et al., 2024). These changes are linked to increased production of metabolites like trimethylamine N-oxide (TMAO), which promotes endothelial dysfunction, fibrosis, and thrombosis. Other taxa enriched in HF, particularly among patients with sarcopenia, include

Nocardiaceae, Pseudonocardiaceae, Alphaproteo-bacteria, Slackia, and Synergistetes (Cienkowski et al., 2024; Peng et al., 2023).

Functionally, reduced SCFAs weaken anti-inflammatory signaling and disrupt gut–cardiovascular protection (Masenga et al., 2023). Meanwhile, elevated level of TMAO and related metabolites worsen vascular inflammation and contribute to adverse cardiac remodeling (Cienkowski et al., 2024). Dysbiosis also alters bile acid metabolism and raises levels of phenylacetylglutamine (PAGln), which increases platelet reactivity and thrombotic risk (Masenga et al., 2023).

Key Microbial Metabolites in HF Pathogenesis

Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate are microbial metabolites generated through fermentation of dietary fibers and resistant starches. Their production depends on the availability of substrates and the presence of fermentative bacteria and enzymes (Frolova et al., 2022).

Acetate is synthesized via the acetyl-CoA pathway by various gut microbes. Propionate is formed through the succinate, acrylate, and propanediol pathways. Butyrate is mainly produced by Firmicutes, such as Faecalibacterium, Roseburia, and Eubacterium, via the butyryl-CoA: acetate CoA-transferase or butyrate kinase pathway (Frolova et al., 2022; Kim, 2021).

HF is associated with reduced SCFA levels, particularly butyrate and propionate, reflecting both gut dysbiosis and impaired intestinal function. In contrast, acetate levels tend to be relatively preserved (Yukino-Iwashita et al., 2022). These reductions correlate with worse HF symptoms, elevated inflammation, poor mental health, and increased sarcopenia risk (Sokolova et al., 2025; Yukino-Iwashita et al., 2022).

SCFAs exert protective effects through multiple mechanism. They activate G-protein-coupled receptors (GPR41, GPR43, GPR109A), reduce inflammation, and preserve barrier integrity (Du et al., 2024; He et al., 2020). SCFAs also inhibit histone deacetylases (HDACs), limiting expression of inflammatory and fibrotic genes and activate Nrf2 signaling, enhancing antioxidant defenses (Du et al., 2024; González-Bosch et al., 2021).

Lower SCFA levels are associated with poor HF prognosis. Restoration of SCFA levels through dietary or microbial interventions improves cardiac function and reduce inflammation (Furukawa et al., 2024; Wang et al., 2023). Thus, SCFAs may serve both as biomarkers and therapeutic targets in HF management (Wang et al., 2023).

Trimethylamine N-Oxide (TMAO)

Trimethylamine N-oxide (TMAO) is a gut-derived metabolite increasingly associated with heart failure (HF). It is synthesized in two steps: gut microbial conversion of dietary compounds into trimethylamine (TMA), followed by hepatic oxidation to TMAO (Simó & García-Cañas, 2020).

TMA is produced from choline (eggs, red meat), L-carnitine (red meat, fish), and betaine (grains, vegetables) by gut microbes via enzymes such as CutC, CntA/B, and GrdH. TMA is then converted into TMAO by hepatic flavin-containing monooxygenases (FMOs) (Simó & García-Cañas, 2020).

HF patients exhibit significantly increased TMAO levels, regardless of ejection fraction (Jarmukhanov et al., 2024). These elevations correlate with higher NYHA class and increased natriuretic peptide levels (Dong et al., 2020). Gut barrier dysfunction in HF may facilitate TMA absorption and TMAO accumulation (Drapała et al., 2020).

TMAO induces inflammation by promoting trained immunity and endothelial activation. It enhances mitochondrial ROS production and ER stress, activates PERK and CREB, and upregulates pro-inflammatory markers such as TNF-α and ICAM-1 (Saaoud et al., 2022). It also inhibits AMPK and SIRT1, exacerbating oxidative stress (Zhou et al., 2022).

TMAO contributes to fibrosis via activation of PERK/Akt/mTOR and the NLRP3 inflammasome, promoting fibroblast activation and extracellular matrix (ECM) deposition (Kapetanaki et al., 2021; Saaoud et al., 2022). It also reprograms metabolism toward glycolysis and impairs lipid handling (Saaoud et al., 2022).

Elevated TMAO independently predicts worse HF outcomes, including increased MACEs and mortality, with a 28–35% higher risk (Zhou et al., 2022). Targeting TMAO through diet, microbial modulation, or enzyme inhibition, may offer therapeutic benefits. Addressing gut dysbiosis and barrier dysfunction is a key strategy in disrupting the gut–heart axis in HF (Jarmukhanov et al., 2024; Organ et al., 2020).

Bile Acids

Beyond their classical roles in fat digestion and cholesterol metabolism, bile acids (BAs) are bioactive signaling molecules that regulate inflammation, fibrosis, and metabolism. Produced through both hepatic synthesis and microbial transformation, BAs serve as a key link between the gut microbiota and heart failure (HF) pathogenesis (Guzior & Quinn, 2021).

The liver converts cholesterol into primary BAs cholic acid (CA) and chenodeoxycholic acid (CDCA), which are conjugated with glycine or taurine and secreted into the intestine (Cai et al., 2022; Guzior & Quinn, 2021). In the gut, bacteria with bile salt hydrolase (BSH) enzymes deconjugate BAs, while other enzymes, including 7α/β-dehydroxylates and hydroxysteroid dehydrogenases, generate secondary BAs such as deoxycholic acid (DCA) and lithocholic acid (LCA) (Guzior & Quinn, 2021; Prete et al., 2020). Some microbes further diversify BAs through novel amino acid conjugation (Guzior & Quinn, 2021).

Patients with HF, especially those with hepatic impairment, exhibit elevated total BA levels and a shift toward more hydrophobic species (De Vries et al., 2024; Vasavan et al., 2020). These BAs exacerbate myocardial stress, inflammation, and fibrosis, whereas hydrophilic BAs like ursodeoxycholic acid (UDCA) may be cardioprotective. Animal studies confirm that excess BAs impair cardiac function, while UDCA can partially reverse these effects (De Vries et al., 2024; Vasavan et al., 2020). Structural cardiac changes and worsened outcomes are linked to elevated BAs, especially in those with coexisting liver disease (De Vries et al., 2024).

BAs modulate inflammation via activation of the NLRP3 inflammasome, while activation of TGR5 receptor exerts anti-inflammatory effects (Feng et al., 2024; Guo et al., 2016). Fibrosis is driven by NLRP3 and IRF3–ZBP1 signaling, counteracted by farnesoid X receptor (FXR) activation (Feng et al., 2024; Guo et al., 2016). Dysregulated BA signaling contributes to the metabolic disturbances seen in HF (Mayerhofer et al., 2017).

Altered BA ratios are linked to poor prognosis, particularly in right-sided HF and coexisting coronary artery disease (Mayerhofer et al., 2017).

Indole-3-Propionic Acid and Other Tryptophan Derivatives

Indole-3-propionic acid (IPA), a microbial metabolite of tryptophan, has emerged as a cardioprotective molecule with antioxidant, anti-inflammatory, and mitochondrial-regulating effects. Decreased IPA levels have been increasingly associated to the pathogenesis of heart failure (HF), especially HF with preserved ejection fraction (HFpEF) (Zünd et al., 2025).

IPA is synthesized from dietary tryptophan by gut microbes, particularly Clostridium spp. and Enterocloster aldenensis, via intermediate conversion to indole-3-lactic acid (ILA), followed by deamination and dehydrogenation (Zünd et al., 2025). Microbial cross-feeding and dietary fiber intake support this process, highlighting the importance of gut diversity in IPA production (Konopelski & Mogilnicka, 2022; Zünd et al., 2025).

Both human and animal studies have shown lower IPA levels in HFpEF and coronary artery disease, correlating with diastolic dysfunction and metabolic derangement (Li et al., 2022; Wang et al., 2024). IPA supplementation improves cardiac performance, reduces oxidative stress, and restores mitochondrial homeostasis via NAD^+/SIRT3 signaling axis (Gesper et al., 2021; Li et al., 2023).

Mechanistically, IPA inhibits NF-κB and NLRP3 inflammasome activity through aryl hydrocarbon receptor (AhR) signaling, downregulating pro-inflammatory cytokines and promoting epigenetic modifications including USP16 methylation and TLR4 ubiquitination (Han et al., 2025; Zhuang et al., 2023). It also enhances mitochondrial respiration and reduces apoptosis in both cardiac and endothelial cells (Gesper et al., 2021).

IPA exerts a context-dependent effect on fibrosis. While it may suppress hepatic stellate cell activation and fibrotic gene expression, it can also activate TGF-β1/Smad signaling in some conditions (Ilha et al., 2025). It supports bone and energy metabolism via mitochondrial and AhR/pregnane X receptor (PXR) pathways (Wang et al., 2024).

Higher IPA levels are associated with improved survival in coronary artery disease (Li et al., 2022). Modulating IPA-producing microbiota offers a promising therapeutic avenue in HF.

Inflammation-Related Metabolites: LPS and IL-22

Inflammation is a major driver of heart failure (HF), with gut-derived molecules like lipopolysaccharide (LPS) and interleukin-22 (IL-22) playing contrasting roles in disease progression (Fatkhullina et al., 2018).

LPS, a structural component of Gram-negative bacteria, is a potent inducer of systemic inflammation. Its levels rise with high-fat diets and dysbiosis, which favor the expansion of LPS-producing microbes (Fatkhullina et al., 2018). IL-22, in contrast, is a host cytokine secreted by type 3 innate lymphoid cells (ILC3) in response to microbial and dietary signals. Microbial antigens stimulate IL-23, which induces IL-22 release, thereby linking the gut microbiota to mucosal immunity (Wang et al., 2025).

In HF, circulating LPS levels are elevated and associated with oxidative stress, inflammation, cardiomyocyte apoptosis, and structural remodeling, including atrial fibrosis and arrhythmogenesis (Wang et al., 2022; Yu et al., 2021). Conversely, IL-22 exerts protective effects in preclinical models by enhancing ventricular function, cardiomyocyte survival, and limiting remodeling through STAT3–FGF21 signaling (Tang et al., 2018).

LPS drives inflammation by reprogramming macrophage metabolism, upregulating the pentose phosphate and serine pathways, and enhancing histone methylation via S-

adenosylmethionine (SAM) (Yu et al., 2019). IL-22 counteracts these effect by inducing autophagy through the ATF4–ATG7 axis and suppressing pro-inflammatory cytokine release (Shao et al., 2020). However, in certain contexts like chronic liver disease, IL-22 may exert profibrotic effect via p38 MAPK–mediated TGF-β signaling (Fabre et al., 2018).

Elevated LPS is associated with adverse HF outcome and may serve as a marker of systemic inflammation (Briasoulis et al., 2016). Although clinical evidence for IL-22 in HF remains limited, its experimental benefits highlight its potential as a therapeutic target within the gut–immune–heart axis.

Gut Dysbiosis and Heart Failure: A Vicious Cycle

Growing evidence supports a bidirectional relationship between gut dysbiosis and heart failure (HF), forming a self-reinforcing loop that accelerates disease progression. This cycle involves gut structural changes, microbial shifts, and systemic inflammation, all of which contribute to worsening cardiac function (Jaimez-Alvarado et al., 2025; Rivera et al., 2024; Trøseid et al., 2020).

HF-induced intestinal hypoperfusion, congestion, and edema compromise gut barrier integrity and motility, creating a microenvironment conducive to microbial imbalance (Branchereau et al., 2019; Lupu et al., 2023; Matacchione et al., 2024). Dysbiosis is marked by a reduction in commensal taxa and an overgrowth of pathobionts, increasing gut permeability and allowing microbial components, particularly lipopolysaccharide (LPS), to enter the circulation (Fountoulakis et al., 2025). This endotoxemia drives chronic inflammation, promotes cardiac fibrosis and remodeling, and further impairs cardiac performance, thereby perpetuating the gut-heart interplay (Carrillo-Salinas et al., 2020).

Preclinical models confirm this vicious cycle. In mice, pressure overload-induced HF induces gut dysbiosis and exacerbates cardiac fibrosis via T cell activation. Gut microbiota depletion protects against fibrosis, while reconstitution restores the pathogenic phenotype (Carrillo-Salinas et al., 2020). Clinically, HF patients show increased intestinal permeability, higher circulating LPS, and disrupted microbiota profiles, features consistently associated with worse cardiac outcomes and elevated inflammation (Fountoulakis et al., 2025; Lupu et al., 2023; Matacchione et al., 2024).

Causal Role of Gut Dysbiosis in HF Progression

Gut dysbiosis is increasingly recognized not merely as a consequence of heart failure (HF), but as a direct contributor to its progression. Emerging evidence highlights its causal role in altering host metabolism, activating immune responses, and promoting cardiac remodeling (Jaimez-Alvarado et al., 2025; Trøseid et al., 2020).

Mendelian randomization studies suggest that specific gut microbes influence HF risk. The presence of Ruminococcus gnavus is associated with increased HF susceptibility, while Faecalibacterium prausnitzii appears exert protective effects (Huang et al., 2025). These microbial shifts affect the balance of key metabolites: reduced short-chain fatty acids (SCFAs) and elevated trimethylamine N-oxide (TMAO) levels are consistently linked to systemic inflammation and impaired cardiac function (Kamo et al., 2017; Lupu et al., 2023).

Dysbiosis also worsens gut barrier dysfunction, facilitating translocation of microbial components and amplifying inflammatory responses (Madan & Mehra, 2020; Muttiah &

Hanafiah, 2025). Clinical studies confirm that microbial composition and metabolite profiles in HF patients correlate with disease severity, inflammatory markers, and prognosis (Kamo et al., 2017; Lupu et al., 2023).

Dysbiosis contributes to HF progression through multiple, interconnected pathways:

1. Systemic inflammation induced by microbial translocation.
2. Metabolite imbalance, marked by reduce protective compounds (e.g., SCFAs, IPA) and increased harmful ones (e.g., TMAO, LPS).
3. Cardiac remodeling and fibrosis, driven by pro-inflammatory and metabolic mediators.

Microbiota-Targeted Interventions in Heart Failure

Recognizing gut dysbiosis as a modifiable factor in heart failure (HF) has spurred interest in microbiota-targeted therapies. These approaches aim to restore microbial balance, reduce harmful metabolites, and modulate host immune and metabolic pathways (Chen et al., 2019; Jia et al., 2019; Yao et al., 2024).

Dietary fiber and prebiotics promote SCFA production, support beneficial microbes, and reduce inflammation (Chen et al., 2019). In HF, high-fiber diets have been shown to lower circulating levels of TMAO and LPS while increasing protective bacterial taxa (Chen et al., 2019; Jia et al., 2019; Yao et al., 2024). Clinical trials report that fiber supplementation improves gut microbial composition and enhances clinical and functional parameters, such as left ventricular ejection fraction (LVEF), 6-minute walk distance, and inflammatory biomarkers (Chen et al., 2023; Li et al., 2025; Luqman et al., 2024).

Probiotic strains, particularly Lactobacillus and Bifidobacterium, may help restore microbial balance and strengthen the intestinal barrier. Early studies suggest modest benefits, including reduced inflammation and improved cardiac markers, but robust randomized trials are still needed to confirm efficacy in HF populations (Chen et al., 2019; Luqman et al., 2024; Mamic et al., 2020).

Targeting microbial enzymes involved in TMA production represents a promising approach to lower TMAO levels. Although this strategy shows cardiovascular benefit in preclinical studies, its effectiveness in HF patients remains to be elucidated (Jia et al., 2019; Mamic et al., 2020; Yao et al., 2024).

Fecal microbiota transplantation (FMT) transfers microbiota from healthy donors to recipients to restore microbial diversity and metabolic function. Preliminary findings suggest FMT improves gut barrier integrity and reduces systemic inflammation, particularly when combined with low-fermentable fiber intake. However, its role in HF remains investigational, with clinical trials currently ongoing (Mocanu et al., 2021; Yuan et al., 2024).

CONCLUSION

The gut-heart axis contributes significantly to heart failure (HF) pathogenesis through a complex interplay of microbial metabolites, immune responses, and systemic inflammation. Key gut-derived compounds such as SCFAs, TMAO, bile acids, IPA, LPS, and IL-22, have distinct effects on cardiac structure and function. Gut dysbiosis, often driven by HF-related intestinal barrier dysfunction, further exacerbates cardiac injury, forming a vicious cycle of disease progression. Microbiota-targeted strategies, particularly dietary fiber-based interventions, show promising benefits in improving gut microbial composition and clinical

outcomes. Other interventions such as probiotics, microbial enzyme inhibitors, and fecal microbiota transplantation are still under active investigation but hold therapeutic potential, though further validation is needed. Future research should focus on clarifying the causal roles of specific microbial taxa in HF progression, identify robust biomarkers of dysbiosis-related cardiac dysfunction, and validate microbiota-directed therapies in well-designed clinical trials. Advancing our understanding of the gut microbiome may offer new opportunities for diagnosis, risk stratification, and personalized treatment in heart failure.

REFERENCES

Jaimez-Alvarado S, López-Tenorio I, Santos JBDL, Bello-Vega DC, Gómez FJR, Amedei A, et al. Gut-Heart Axis: Microbiome Involvement in Restrictive Cardiomyopathies. Biomedicines. 2025; 13(1):1-19

Trøseid M, Andersen G, Broch K, Hov J. The gut microbiome in coronary artery disease and heart failure: Current knowledge and future directions. EBioMedicine. 2020; 52: 1-10

Rivera K, González L, Bravo L, Manjarrés L, Andia M. The Gut–Heart Axis: Molecular Perspectives and Implications for Myocardial Infarction. Int J Mol Sci. 2024; 25:1-25

Witkowski M, Weeks T, Hazen S. Gut Microbiota and Cardiovascular Disease. Circ Res. 2020; 127:553–70.

Hao R, Zheng Y, Zhao Q, Chen J, Fan R, Chen P, et al. Evaluation value of ultrasound on gastrointestinal function in patients with acute heart failure. Front Cardiovasc Med. 2024; 11:1-12

Perticone M, Gigliotti S, Shehaj E, Maio R, Suraci E, Miceli S, et al. Gut Permeability and Immune-Mediated Inflammation in Heart Failure. Biomedicines. 2024; 12(6):1-12

Xiao JH, Wang Y, Zhang XM, Wang WX, Zhang Q, Tang Y, et al. Intestinal permeability in human cardiovascular diseases: a systematic review and meta-analysis. Front Nutr. 2024; 11:1-10

Fountoulakis P, Theofilis P, Vlachakis P, Karakasis P, Pamporis K, Sagris M, et al. Gut Microbiota in Heart Failure-The Role of Inflammation. Biomedicines. 2025; 13:1-25

Sun X. Research Status and Trends of Gut Microbiota and Intestinal Diseases Based on Bibliometrics. Microorganisms. 2025; 13:1-23

Cienkowski K, Cienkowska A, Kupczyńska K, Bielecka-Dabrowa A. The Role of Gut Microbiota and Its Metabolites in Patients with Heart Failure. Biomedicines. 2024; 12:1-18

Nemet I, Saha P, Gupta N, Zhu W, Romano K, Skye S, et al. A Cardiovascular Disease-Linked Gut Microbial Metabolite Acts via Adrenergic Receptors. Cell. 2020;180:862–77.

Drapała A, Szudzik M, Chabowski D, Mogilnicka I, Jaworska K, Kraszewska K, et al. Heart Failure Disturbs Gut–Blood Barrier and Increases Plasma Trimethylamine, a Toxic Bacterial Metabolite. Int J Mol Sci. 2020; 21:1-15

Lupu V, Răileanu AA, Mihai C, Morariu I, Lupu A, Stârcea I, et al. The Implication of the Gut Microbiome in Heart Failure. Cells. 2023; 12:1-24

Paolillo R, Boccella N, Coretti L, D'apice S, Lama A, Schiattarella G, et al. Transverse aortic constriction impairs intestinal barrier integrity, promotes inflammation and alterations in gut microbiota composition. Eur Heart J. 2020; 41:1

Peng J, Gong H, Lyu X, Liu Y, Li S, Tan S, et al. Characteristics of the fecal microbiome and metabolome in older patients with heart failure and sarcopenia. Front Cell Infect Microbiol. 2023; 13:1-10

Masenga S, Povia J, Lwiindi P, Kirabo A. Recent Advances in Microbiota-Associated Metabolites in Heart Failure. Biomedicines. 2023; 11:1-22

Frolova M, Suvorova I, Iablokov S, Petrov S, Rodionov D. Genomic reconstruction of short-chain fatty acid production by the human gut microbiota. Front Mol Biosci. 2022; 9:1-25

Kim C. Control of lymphocyte functions by gut microbiota-derived short-chain fatty acids. Cell Mol Immunol. 2021;18:1161–71.

Yukino-Iwashita M, Nagatomo Y, Kawai A, Taruoka A, Yumita Y, Kagami K, et al. Short-Chain Fatty Acids in Gut–Heart Axis: Their Role in the Pathology of Heart Failure. J Pers Med. 2022; 12:1-13

Sokolova A, Dragunov D, Klimova A, Golubev Ya, Shmigol T, Negrebetsky V, et al. Diagnostic Role of Various Short-Chain Fatty Acids in Blood of Patients with Chronic Heart Failure Complicated by Sarcopenia. Russ J Gastroenterol Hepatol Coloproctology. 2025; 35(1):42-52

He J, Zhang P, Shen L, Niu L, Tan Y, Chen L, et al. Short-Chain Fatty Acids and Their Association with Signalling Pathways in Inflammation, Glucose and Lipid Metabolism. Int J Mol Sci. 2020; 21: 1-16

Du Y, He C, An Y, Huang Y, Zhang H, Fu WX, et al. The Role of Short Chain Fatty Acids in Inflammation and Body Health. Int J Mol Sci. 2024; 25(13):1-23

González-Bosch C, Boorman E, Zunszain P, Mann G. Short-chain fatty acids as modulators of redox signaling in health and disease. Redox Biol. 2021; 47:1-11

Furukawa N, Kobayashi M, Ito M, Matsui H, Ohashi K, Murohara T, et al. Soy protein β-conglycinin ameliorates pressure overload-induced heart failure by increasing short-chain fatty acid (SCFA)-producing gut microbiota and intestinal SCFAs. Clin Nutr. 2024;43 12:124–37.

Wang L, Cai Y, Garssen J, J. Henricks PA, Folkerts G, Braber S. The Bidirectional Gut–Lung Axis in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2023; 207(9): 1146-60

Simó C, García-Cañas V. Dietary bioactive ingredients to modulate the gut microbiota-derived metabolite TMAO. New opportunities for functional food development. Food Funct. 2020; 11:6745-76

Jarmukhanov Z, Mukhanbetzhanov N, Kozhakhmetov S, Nurgaziyev M, Sailybayeva A, Bekbossynova M, et al. The association between the gut microbiota metabolite trimethylamine N-oxide and heart failure. Front Microbiol. 2024; 15:1-10

Dong Z, Liang Z, Wang X, Liu W, Zhao L, Wang S, et al. The correlation between plasma trimethylamine N-oxide level and heart failure classification in northern Chinese patients. Ann Palliat Med. 2020; 9(5):2862-71

Saaoud F, Liu L, Xu K, Cueto R, Shao Y, Lu Y, et al. Aorta- and liver-generated TMAO enhances trained immunity for increased inflammation via ER stress/mitochondrial ROS/glycolysis pathways. JCI Insight. 2022; 8(1):1-22

Zhou S, Xue J, Shan J, Hong YS, Zhu W, Nie ZY, et al. Gut-Flora-Dependent Metabolite Trimethylamine-N-Oxide Promotes Atherosclerosis-Associated Inflammation Responses by Indirect ROS Stimulation and Signaling Involving AMPK and SIRT1. Nutrients. 2022; 14:1-20

Kapetanaki S, Kumawat A, Persson K, Demirel I. The Fibrotic Effects of TMAO on Human Renal Fibroblasts Is Mediated by NLRP3, Caspase-1 and the PERK/Akt/mTOR Pathway. Int J Mol Sci. 2021; 22:1-15

Organ C, Li Z, Sharp T, Polhemus D, Gupta N, Goodchild T, et al. Nonlethal Inhibition of Gut Microbial Trimethylamine N-oxide Production Improves Cardiac Function and Remodeling in a Murine Model of Heart Failure. J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2020; 9:1-15

Guzior D, Quinn R. Review: microbial transformations of human bile acids. Microbiome. 2021;9(140): 1-13

Cai J, Rimal B, Jiang C, Chiang J, Patterson A. Bile acid metabolism and signaling, the microbiota, and metabolic disease. Pharmacol Ther. 2022; 237:1-55

Prete R, Long S, Gallardo A, Gahan C, Corsetti A, Joyce S. Beneficial bile acid metabolism from Lactobacillus plantarum of food origin. Sci Rep. 2020 Jan 24; 10:1-11

De Vries H, Eijgenraam T, Bloks V, Mulder N, Van Zutphen T, Silljé H, et al. Elevated plasma bile acids coincide with cardiac stress and inflammation in young Cyp2c70−/− mice. Pediatr Res. 2024; 97:2145–52.

Vasavan T, Deepak S, Jayawardane I, Lucchini M, Martin C, Geenes V, et al. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. J Hepatol. 2020; 74:1087–96.

Guo C, Xie S, Chi Z, Zhang J, Liu Y, Zhang L, et al. Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome. Immunity. 2016; 45 4:802–16.

Feng S, Xie XM, Li J, Xu X, Chen CY, Zou G, et al. Bile acids induce liver fibrosis through the NLRP3 inflammasome pathway and the mechanism of FXR inhibition of NLRP3 activation. Hepatol Int. 2024; 18:1040–52.

Mayerhofer C, Ueland T, Broch K, Vincent R, Cross G, Dahl C, et al. Increased Secondary/Primary Bile Acid Ratio in Chronic Heart Failure. J Card Fail. 2017; 23 9:666–71.

Zünd J, Mujezinovic D, Reichlin M, Plüss S, Caflisch M, Robinson S, et al. Novel cross-feeding human gut microbes metabolizing tryptophan to indole-3-propionate. Gut Microbes. 2025; 17(1):1-16

Konopelski P, Mogilnicka I. Biological Effects of Indole-3-Propionic Acid, a Gut Microbiota-Derived Metabolite, and Its Precursor Tryptophan in Mammals' Health and Disease. Int J Mol Sci. 2022; 23:1-19

Li Q, You Y, Zeng Y, Wang X, Pan Z, Pang J, et al. Associations between plasma tryptophan and indole-3-propionic acid levels and mortality in patients with coronary artery disease. Am J Clin Nutr. 2022; 116:1070-77

Wang YC, Koay Y, Pan C, Zhou Z, Tang W, Wilcox J, et al. Indole-3-Propionic Acid Protects Against Heart Failure with Preserved Ejection Fraction. Circ Res. 2024; 134:371–89.

Li C, Chang J, Wang Y, Pan G. Indole-3-propionic acid, a product of intestinal flora, inhibits the HDAC6/NOX2 signaling and relieves doxorubicin-induced cardiomyocyte damage. Folia Morphol. 2023; 83(2):382-390

Gesper M, Nonnast A, Kumowski N, Stoehr R, Schuett K, Marx N, et al. Gut-Derived Metabolite Indole-3-Propionic Acid Modulates Mitochondrial Function in Cardiomyocytes and Alters Cardiac Function. Front Med. 2021; 8: 1-18

Han Z, Fu J, Gong A, Ren W. Bacterial indole-3-propionic acid inhibits macrophage IL-1β production through targeting methionine metabolism. Sci China Life Sci. 2025; 68(4):1118-31

Zhuang H, Ren X, Jiang F, Zhou P. Indole-3-propionic acid alleviates chondrocytes inflammation and osteoarthritis via the AhR/NF-κB axis. Mol Med. 2023; 29(17):1-13

Ilha M, Sehgal R, Matilainen J, Rilla K, Kaminska D, Gandhi S, et al. Indole-3-propionic acid promotes hepatic stellate cells inactivation. J Transl Med. 2025;23(253):1-18

Fatkhullina A, Peshkova I, Dzutsev A, Aghayev T, McCulloch J, Thovarai V, et al. An Interleukin-23-Interleukin-22 Axis Regulates Intestinal Microbial Homeostasis to Protect from Diet-Induced Atherosclerosis. Immunity. 2018; 49(5):943-957

Wang Y, Allan D, Gewirtz A. Microbiota-derived proteins synergize with IL-23 to drive IL22 production in model type 3 innate lymphoid cells. PLOS ONE. 2025;20(1):1-12

Yu Y, Hu LL, Liu L, Yu LL, Li JP, Rao J, et al. Hsp22 ameliorates lipopolysaccharide-induced myocardial injury by inhibiting inflammation, oxidative stress, and apoptosis. Bioengineered. 2021; 12:12544–54.

Wang M, Xiong H, Lu L, Zhu T, Jiang H. Serum Lipopolysaccharide Is Associated with the Recurrence of Atrial Fibrillation after Radiofrequency Ablation by Increasing Systemic Inflammation and Atrial Fibrosis. Oxid Med Cell Longev. 2022; 2022:1-7

Tang T, Li Y, Li JJ, Wang K, Han Y, Dong WY, et al. Liver-heart crosstalk controls IL-22 activity in cardiac protection after myocardial infarction. Theranostics. 2018; 8:4552–62.

Yu W, Wang Z, Zhang K, Chi Z, Xu T, Jiang D, et al. One-Carbon Metabolism Supports S-Adenosylmethionine and Histone Methylation to Drive Inflammatory Macrophages. Mol Cell. 2019; 75:1147-60

Shao L, Xiong X, Zhang Y, Miao H, Ren YQ, Tang X, et al. IL-22 ameliorates LPS-induced acute liver injury by autophagy activation through ATF4-ATG7 signaling. Cell Death Dis. 2020; 11:1-12

Fabre T, Molina M, Soucy G, Goulet J, Willems B, Villeneuve J, et al. Type 3 cytokines IL-17A and IL-22 drive TGF-β–dependent liver fibrosis. Sci Immunol. 2018; 3(28):1-10

Briasoulis A, Androulakis E, Christophides T, Tousoulis D. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. Heart Fail Rev. 2016;21:169–76.

Branchereau M, Burcelin R, Heymes C. The gut microbiome and heart failure: A better gut for a better heart. Rev Endocr Metab Disord. 2019;20:407–14.

Matacchione G, Piacenza F, Pimpini L, Rosati Y, Marcozzi S. The role of the gut microbiota in the onset and progression of heart failure: insights into epigenetic mechanisms and aging. Clin Epigenetics. 2024; 16:1-17

Carrillo-Salinas F, Anastasiou M, Ngwenyama N, Kaur K, Tai A, Smolgovsky S, et al. Gut dysbiosis induced by cardiac pressure overload enhances adverse cardiac remodeling in a T cell-dependent manner. Gut Microbes. 2020; 12(1):1-21

Huang L, Zhao X, Wang J, Guan J, Huang B, Feng J, et al. Gut microbiota and risk of heart failure in European population-A comprehensive Mendelian randomization study. ESC Heart Fail. 2025; 2025:1-10

Kamo T, Akazawa H, Suda W, Saga-Kamo A, Shimizu Y, Yagi H, et al. Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. PLoS ONE. 2017; 12(3):1-14

Madan S, Mehra M. Gut dysbiosis and heart failure: navigating the universe within. Eur J Heart Fail. 2020; 22:629-637

Muttiah B, Hanafiah A. Gut Microbiota and Cardiovascular Diseases: Unraveling the Role of Dysbiosis and Microbial Metabolites. Int J Mol Sci. 2025 Apr 30; 26:1-34

Chen X, Li H, Hu X, Zhang Y, Zhang SY. Current understanding of gut microbiota alterations and related therapeutic intervention strategies in heart failure. Chin Med J (Engl). 2019;132:1843–55.

Yao F, Liu C, Luo D, Zhou YL, Li Q, Huang H, et al. Metabolites of Microbiota: A Novel Therapy for Heart Disease. Food Rev Int. 2024;41:1099–115.

Jia Q, Li H, Zhou H, Zhang X, Zhang A, Xie Y, et al. Role and Effective Therapeutic Target of Gut Microbiota in Heart Failure. Cardiovasc Ther. 2019; 2019:1-10

Li L, Yang L, Liu M. The effect of high-fiber diet based on gut microbiota in patients with chronic heart failure. Physiol Genomics. 2025; 57:140-145

Chen Z, Liang W, Liang J, Dou J, Guo F, Zhang D, et al. Probiotics: Functional Food Ingredients with the Potential to Reduce Hypertension. Front Cell Infect Microbiol. 2023; 13:1-14

Luqman A, Hassan A, Ullah M, Naseem S, Ullah M, Zhang L, et al. Role of the intestinal microbiome and its therapeutic intervention in cardiovascular disorder. Front Immunol. 2024; 15:1-24

Mamic P, Chaikijurajai T, Tang W. Gut microbiome - A potential mediator of pathogenesis in heart failure and its comorbidities: State-of-the-art review. J Mol Cell Cardiol. 2020; 152:105-117

Mocanu V, Zhang Z, Deehan E, Kao D, Hotte N, Karmali S, et al. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. Nat Med. 2021; 27:1272–9.

Yuan L, Li Y, Chen M, Xue L, Wang J, Ding Y, et al. Therapeutic applications of gut microbes in cardiometabolic diseases: current state and perspectives. Appl Microbiol Biotechnol. 2024; 108:1-21