Clinical Epigenetics

REVIEW

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The role of the gut microbiota in the onset and progression of heart failure: insights into epigenetic mechanisms and aging

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Abstract

Background The gut microbiota (GM) plays a critical role in regulating human physiology, with dysbiosis linked to various diseases, including heart failure (HF). HF is a complex syndrome with a significant global health impact, as its incidence doubles with each decade of life, and its prevalence peaks in individuals over 80 years. A bidirectional interaction exists between GM and HF, where alterations in gut health can worsen the disease's progression.

Main body The "gut hypothesis of HF" suggests that HF-induced changes, such as reduced intestinal perfusion and altered gut motility, negatively impact GM composition, leading to increased intestinal permeability, the release of GM-derived metabolites into the bloodstream, and systemic inflammation. This process creates a vicious cycle that further deteriorates heart function. GM-derived metabolites, including trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and secondary bile acids (BAs), can influence gene expression through epigenetic mechanisms, such as DNA methylation and histone modifications. These epigenetic changes may play a crucial role in mediating the effects of dysbiotic gut microbial metabolites, linking them to altered cardiac health and contributing to the progression of HF. This process is particularly relevant in older individuals, as the aging process itself has been associated with both dysbiosis and cumulative epigenetic alterations, intensifying the interplay between GM, epigenetic changes, and HF, and further increasing the risk of HF in the elderly.

Conclusion Despite the growing body of evidence, the complex interplay between GM, epigenetic modifications, and HF remains poorly understood. The dynamic nature of epigenetics and GM, shaped by various factors such as age, diet, and lifestyle, presents significant challenges in elucidating the precise mechanisms underlying this complex relationship. Future research should prioritize innovative approaches to overcome these limitations. By identifying specific metabolite-induced epigenetic modifications and modulating the composition and function of GM, novel and personalized therapeutic strategies for the prevention and/or treatment of HF can be developed. Moreover, targeted research focusing specifically on older individuals is crucial for understanding the intricate connections between GM, epigenetics, and HF during aging.

Keywords Heart failure, Gut microbiome, Dysbiosis, Epigenetic changes, Aging

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Background

Accumulating evidence has established the gut microbiota (GM) as a pivotal regulator of human physiological processes [1–4]. In light of the significant connection between GM and host health, research increasingly shows that alterations in GM composition and function, a phenomenon known as dysbiosis, play a critical role in the pathogenesis and worsening of a wide range of host diseases, including cardiovascular diseases (CVD) [5–8]. Dysbiosis has been linked to inflammation, oxidative stress, and metabolic disruptions, all of which can exacerbate CVD. Several studies have demonstrated that interventions with probiotics, prebiotics, and targeted microbiome manipulation have a positive indirect impact on various CVD risk factors (including Type II diabetes mellitus, hypercholesterolemia, hypertension, and obesity) [9, 10]. These findings suggest that restoring gut homeostasis may help mitigate inflammation and other CVD-related pathological processes [11, 12].

Heart failure (HF), a complex clinical syndrome characterized by the inability of the heart to adequately pump blood, has become a significant public health concern globally, standing as a leading cause of morbidity and mortality. According to recent estimates, the global burden of HF is staggering, affecting at least 56 million people worldwide, a number expected to increase with population aging [13]. The incidence of HF doubles with each decade of life, with prevalence reaching nearly 10% in individuals over 80 years of age, posing age as a crucial risk factor for the onset and progression of this condition [14].

Increasing evidence supports the idea of a close relationship between HF and the GM. According to the "gut hypothesis of HF", the altered intestinal environment associated with HF—such as reduced blood flow, intestinal edema, and changes in gut motility—can alter the composition of the microbiota, which in turn may worsen the clinical course of the disease [15]. Dysbiosis has been shown to trigger systemic inflammation, oxidative stress, and metabolic disturbances, all of which contribute to the onset of HF [16]. This creates a bidirectional relationship between the GM and HF.

Besides this, growing evidence highlights that GM influences not only metabolic and inflammatory responses but also has a direct impact on gene regulation through epigenetic mechanisms [17, 18]. These interactions add another layer of complexity to the relationship between gut health and cardiovascular function.

This framework becomes even more significant in the context of aging. The aging process itself is intimately linked to GM dysbiosis, as significant changes in microbial diversity and community structure are observed in older individuals. Epigenetic alterations also accumulate with age and are thought to play a crucial role in the onset of numerous age-related diseases, including HF [19–23]. Therefore, understanding the intricate connections between GM, epigenetics, and HF in elderly populations is essential for addressing the rising burden of CVD during aging.

In this review, we will explore emerging evidence regarding the interplay between GM, epigenetic modifications, and HF, with a particular focus on aging.

Heart failure: definition, epidemiology and pathogenesis

HF represents a complex clinical syndrome resulting from structural or functional cardiac abnormalities that impair the heart's ability to pump blood effectively. This condition leads to chronic tissue hypoperfusion, manifesting in a range of clinical symptoms that initially occur during strenuous physical activity but progressively worsen to the point of occurring even at rest.

The pathophysiology of HF is intricate, involving a series of events, including fluid leakage into surrounding tissues, culminating in pulmonary edema and other complications [24]. Acute HF, a critical variant frequently associated with acute coronary syndrome, is characterized by a sudden deterioration in ventricular function, resulting in inadequate tissue perfusion. This acute form may arise from an exacerbation of chronic HF, underscoring the dynamic nature of the disease. The role of inflammatory markers is pivotal in the pathogenesis of HF, highlighting the interplay between systemic inflammation and cardiovascular health [25].

The etiology of HF is predominantly linked to myocardial dysfunction, which can be systolic, diastolic, or both. This dysfunction is often a consequence of underlying conditions such as coronary artery disease, hypertension, diabetes, dyslipidemia, and obesity. Additionally, age-related changes in vascular compliance and arterial stiffness contribute to the progression of the disease, promoting vascular remodeling and fibrosis. These changes precede hypertension and accelerate other vascular diseases, such as atherosclerosis, thereby increasing the risk of stroke and myocardial infarction. Moreover, HF induces chronic renal hypoperfusion, which activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, fostering a pro-inflammatory, profibrotic, and hypertrophic environment that exacerbates both cardiovascular and renal dysfunction [26].

HF reveals a decreasing incidence but an increasing prevalence, largely attributed to population aging and advances in treatment [27]. Indeed, HF is particularly prevalent among older adults, significantly impacting morbidity, mortality, and healthcare costs [28]. In Italy, HF accounts for approximately 200,000 hospitalizations

annually, predominantly affecting individuals over 65 years of age [29]. This epidemiological trend underscores the necessity for comprehensive management strategies that address the diverse and evolving nature of HF, integrating advancements in pharmacological treatment alongside a deeper understanding of the disease's underlying mechanisms [30].

The "gut hypothesis of HF"

The "gut hypothesis of HF" posits a bidirectional interaction between the heart and the health of the GM [31–33]. While HF can negatively influence the composition and function of the GM, the GM, in turn, can significantly impact the progression and severity of HF, giving rise to a vicious cycle (Fig. 1).

Hemodynamic derangements in HF may lead to reduced intestinal perfusion, resulting in ischemia and damage to the intestinal barrier. This phenomenon can lead to changes in gut luminal pH and hypoxia, disrupting the normal composition of the GM: indeed, a prevalent pattern observed in the GM of HF patients is a transition toward pathogenic phyla and a reduction in the abundance of beneficial bacteria. These pathogenic bacteria can produce harmful substances, such as endotoxins like lipopolysaccharide (LPS), as well as other metabolites that further compromise the integrity of the intestinal barrier.

Increased intestinal permeability, commonly referred to as "leaky gut", allows bacteria, bacterial metabolites, and endotoxins to translocate into the bloodstream, triggering a systemic inflammatory response that directly damages cardiomyocytes [34]. The resulting systemic inflammation and oxidative stress, all known risk factors for HF [33], can worsen the hemodynamic instability in HF, creating a vicious cycle that exacerbates the condition [35].

Gut microbiota and heart failure: a bidirectional relationship

Several studies have reported differences in the composition and function of GM between HF patients and healthy subjects [36, 37]. A recent study based on culture-dependent methods found that adult patients with chronic HF had intestinal overgrowth of pathogenic bacteria (such as *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, and *Candida)* and increased intestinal permeability respect to healthy adults. Additionally, the development rate of *Candida, Campylobacter*, and *Shigella* species correlated with HF severity [38]. Similarly, other studies observed significant differences in the composition of fecal microbes between severe chronic HF adult patients and healthy controls: the significantly reduced α-diversity, a major indicator to describe the diversity of the GM, observed in HF patients suggested a notable loss of gut flora biodiversity associated with the disease [39–41]. More specifically, this disruption in microbial diversity was characterized by a marked Gut pathogen overgrowth such as those from the Proteobacteria phylum, and a concurrent decline in "beneficial" gut microbes such as *Bifidobacterium* or those from the Firmicutes phylum (including *Faecalibacterium*, *Eubacterium*, and *Dorea*), all of which have anti-inflammatory effects [40–42]. Table 1 summarizes studies on GM in patients with HF.

Supporting the involvement of the GM in the pathophysiology of HF, several studies in animal models reported the positive impact of probiotics and prebiotics administration and of targeted microbiome manipulation on cardiac remodeling by potentially affecting inflammatory pathways and metabolic processes linked to cardiovascular health [43]. Lam et al., first provided evidence that probiotics supplementation may offer cardioprotective benefits in animal models: they reported a reduction in infarct size and improved left ventricular function in ischemic rats treated with the probiotic *Lactobacillus plantarum* 24 h before coronary artery ligation [44]. Accordingly, *Lactobacillus rhamnosus* GR-1 [45] or *Lactobacillus johnsonii* [46] treatment of rats subjected to coronary artery occlusion significantly attenuated left ventricular hypertrophy and improved hemodynamic parameters. Also, *Lactobacillus vaginalis* improved cardiac function and decreased cardiac infarct size in mice [47].

Prophylactic administration of *Lactobacillus reuteri*, its metabolite GABA, *Bifidobacterium infantis,* or its metabolite inosine mitigated macrophage-mediated cardiac inflammation, thereby alleviating cardiac dysfunction and heart injury in animals subjected to acute ischemic cardiac injury [48, 49]. Additionally, long-term kefir treatment was shown to reduce blood pressure through reduction of cardiac hypertrophy, improvement of cardiac contractility and calcium-handling proteins, and a decrease in central nervous system regulation of sympathetic activity [50].

However, our knowledge regarding the effects of probiotic and prebiotic treatment in patients with HF is limited and has produced mixed results. For instance, the administration of the probiotic *Lactobacillus rhamnosus* GG in patients with recent myocardial infarction led to improvements in echocardiographic indices, as well as improvements in metabolic profiles and inflammatory markers [51]. Similarly, oral administration of the probiotic *Saccharomyces boulardii* in a small cohort of HF patients resulted in a significant reduction in left atrial diameter and improvement in left ventricular ejection fraction (LVEF) compared to the placebo group

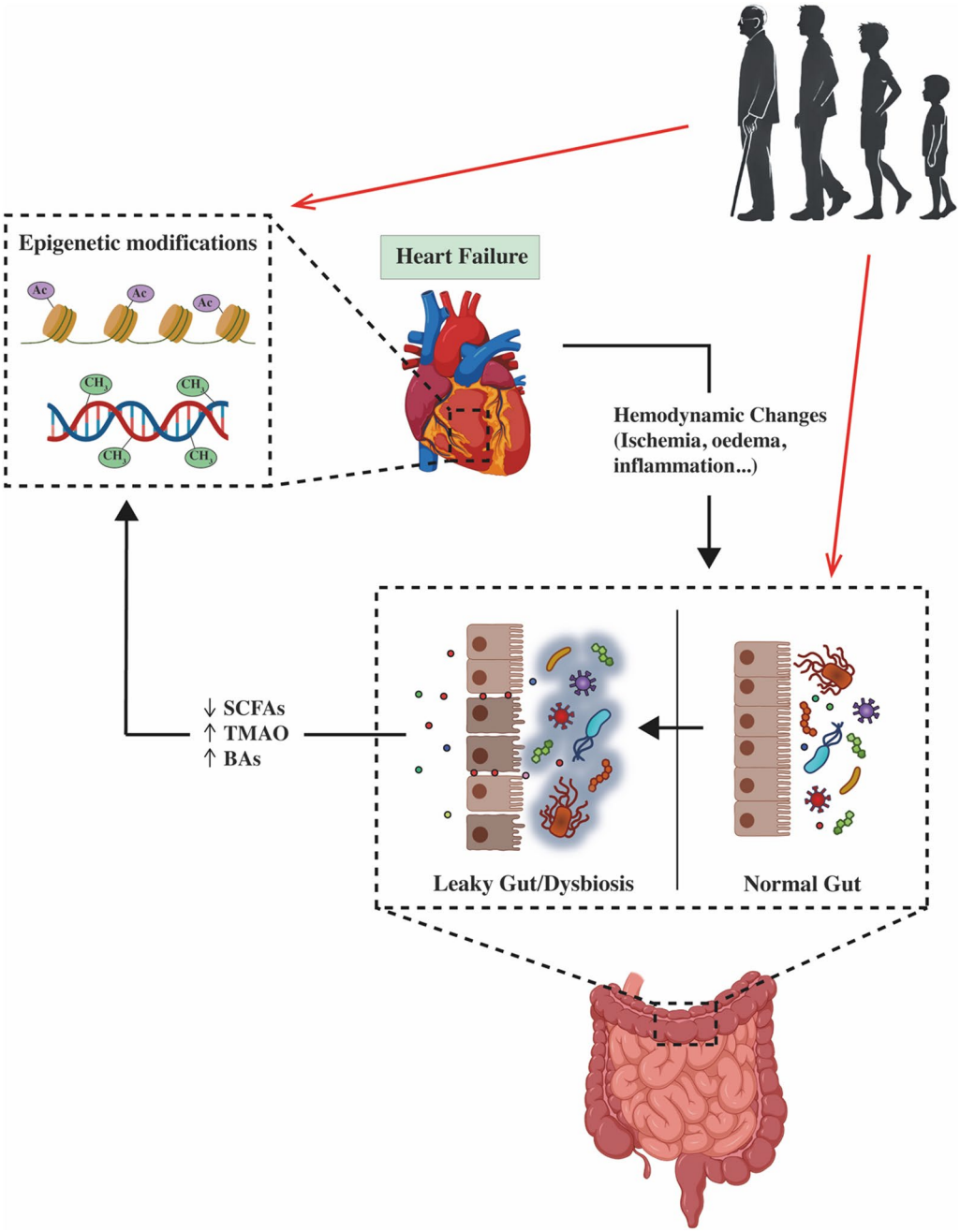

Fig. 1 Epigenetic modifications mediate the gut-heart axis in Heart Failure. Hemodynamic changes in HF may lead to reduced intestinal perfusion, contributing to intestinal barrier dysfunction (leaky gut) and dysbiosis. These, in turn, result in altered gut microbial metabolite production and release in the bloodstream. Decreased levels of short-chain fatty acids (SCFAs) and increased levels of trimethylamine N-oxide (TMAO) and secondary Bile Acids (BAs), contribute to systemic inflammation and cardiovascular complications. Epigenetic changes can act as key modulators in this relationship, as these GM-derived metabolites can influence gene expression through DNA methylation and histone modifications in cardiac cells. The aging process can influence GM dysbiosis and epigenetic changes

[52]. However, in the GutHeart trial, the authors did not observe a clinically significant effect on LVEF following the administration of *S. boulardii* in a larger cohort of HF patients [53]. An overview of studies investigating the impact of probiotic administration on HF in both murine models and human subjects is provided in Table 2.

Another increasingly studied component of the GM is the virome, which primarily consists of bacteriophages (commonly referred to as the phagome). These phages

Table 1 Key studies highlighting changes in GM composition in HF patients

Author [refs]	Study population	Molecular technique	Microbiota profile
Pasini et al. [38]	Chronic HF	Traditional Culture Techniques	↑ *Campylobacter, Shigella, Salmonella, Yersinia enterolytica, Candida*
Luedde et al. [39]	Chronic HF	Bacterial 16S rRNA gene sequencing	↓ *Coriobacteriaceae, Erysipelotrichaceae, Ruminococcaceae*
Kummen et al. [40]	Chronic HF	Bacterial 16S rRNA gene sequencing	↓ *Lachnospiraceae*
Sun et al. [41]	Severe Chronic HF	Bacterial 16S rRNA gene sequencing	↓ *Ruminococcaceae, Lachnospiraceae, Dialister* ↑ *Proteobacteria, Enterococcaceae*
Cui et al. [42]	Chronic HF	Bacterial 16S rRNA gene sequencing	↓ *Faecalibacterium prausnitzii* ↑ *Ruminococcus gnavus*

Table 2 Impact of probiotic administration on HF in animal models and human subjects

Author [refs]	Population		Probiotic supplementation	Significant findings
	Species	Patient/Model		
Lam et al. [44]	Rat	Coronary artery ligation	*Lactobacillus plantarum* 299v	↓ cardiac infarct size; ↑ left ventricular function
Gan et al. [45]	Rat	Coronary artery ligation	*Lactobacillus rhamnosus* GR-1	↓ left ventricular hypertrophy; ↑ hemodynamic parameters
Zhong et al. [46]	Rat	Coronary artery ligation	*Lactobacillus johnsonii*	↓ left ventricular hypertrophy; ↑ hemodynamic parameters; Remodeling of GM
Li et al. [47]	Mouse	Coronary artery ligation	*Lactobacillus vaginalis*	↓ cardiac infarct size; ↑ cardiac function
Zhang et al [48]	Mouse	Coronary artery ligation	*Bifidobacterium infantis* or its metabolite inosine	↓ cardiac infarct size; ↑ cardiac function
Wang et al [49]	Mouse	Coronary artery ligation	*Lactobacillus reuteri* or its metabolite GABA	↓ cardiac infarct size and macrophage-mediated cardiac inflammation; ↑ cardiac function
Silva-Cutini et al. [50]	Rat	Spontaneously hypertensive rats	kefir	↓ cardiac hypertrophy; ↑ cardiac function, hemodynamic parameters, cardiac contractility
Moludi et al [51]	Human	Myocardial infarction	*Lactobacillus rhamnosus* GG	↓ inflammatory biomarkers; ↑ echocardiographic indices
Costanza et al [52]	Human	Chronic HF	*Saccharomyces boulardii*	↓ inflammatory biomarkers; ↑ echocardiographic indices
Awoyemi et al [53]	Human	Chronic HF	*Saccharomyces boulardii*	No clinical effect

represent the vast majority of the virome and play a significant role in shaping microbial communities and influencing gut health [54]. A compositional analysis of the gut virome of patients with coronary heart disease (CHD), identified a higher proportion of Virgaviridae, a family of rod-shaped plant viruses, and a reduction in Microviridae in individuals with CHD compared to control groups [55]. However, information about the characteristics of the gut phagome in relation to CVD, and in particular to HF, is still insufficient, and the underlying mechanisms driving these alterations remain to be explored.

Overall, despite the well-documented bidirectional interaction between the heart and the GM, and the potential of probiotics and prebiotics as therapeutic agents for HF, the mixed outcomes obtained in clinical trials highlight the need for more extensive and well-designed research. Further studies are required to clarify their efficacy and better understand the specific

conditions under which probiotic and prebiotic treatments may be most effective.

The "leaky gut": a gateway to systemic inflammation and HF

Having established the bidirectional relationship between the GM and HF, we now turn our attention to the mechanisms by which dysbiosis and increased intestinal permeability can contribute to the progression of this condition.

The intestinal mucosa and the epithelial layer act as a critical defense, shielding the body's inner organs from the harmful contents of the gut. When in a healthy state, intestinal barrier functionality is preserved by the apical junctional complex between epithelial cells and mucus secretion. Goblet cells secrete mucins that act as a protective barrier, halting the progress of bacteria and large particles toward the epithelial layer. The apical junctional complex, composed of tight junctions, adherens junctions, and desmosomes, regulates the flow of water and nutrients through the epithelium.

Key proteins involved in tight junction (TJP), including occludin, claudin, zonula occludens, and junctional adhesion molecules, are crucial in managing cell–cell communication and controlling paracellular permeability to uphold the function of epithelial barriers. Disruption of TJPs can lead to increased intestinal permeability, allowing large molecules and bacteria to pass through the epithelial barrier, which contributes to the onset and progression of disease [56].

HF has been linked to changes in intestinal permeability: systemic congestion in HF can lead to intestinal hypoperfusion, endothelial cells dysfunction, and increased intestinal permeability [57]. This results in bacteria and bacterial products entering the bloodstream, triggering systemic inflammation—a hallmark of HF believed to contribute to its progression [58].

In patients with HF, the presence of bacterial DNA in peripheral blood is linked to significantly elevated levels of inflammatory markers, including hypersensitive C-reactive protein and interleukin (IL)-6. LPS, a toxic and immunogenic component of gram-negative bacteria, also enters the bloodstream through the damaged intestinal wall and acts as a strong activator of pro-inflammatory cytokines in HF patients. By binding to Toll-like receptor 4 on cardiomyocytes, cardiac fibroblasts, and macrophages, it can trigger the release of various inflammatory mediators, giving rise to a robust inflammatory response [59, 60]. Additionally, LPS-mediated activation of the NLRP3 inflammasome is crucial for myocardial damage, with interleukin-1β (IL-1β) and IL-18 as key downstream factors [61]. Chronic low-grade inflammation, a hallmark of many chronic diseases including HF, is believed to be driven in part by this ongoing exposure to bacterial products.

In addition to LPS, other bacterial metabolites that enter the bloodstream through the damaged intestinal wall in the leaky gut include trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and secondary bile acids are released into circulation due to increased intestinal permeability [2, 42, 62, 63]. TMAO has been associated with a higher risk of cardiovascular outcomes, while SCFAs can influence inflammation and immune responses, and bile acids can impact lipid and glucose metabolism, further affecting cardiovascular function [62].

Research indicates that serum concentrations of several cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF), are elevated in HF patients and correlate with more severe clinical manifestations and reduced survival rates. Additionally, these cytokines play a role in cardiomyocyte apoptosis, hypertrophy, and fibrosis, exacerbating the overall condition of the heart. Increased intestinal permeability, therefore, exacerbates systemic inflammation, creating a vicious cycle that compromises both gut and cardiovascular health [57].

In support, research has shown a long-standing connection between intestinal problems and HF, particularly with conditions like inflammatory bowel disease increasing the chances of heart issues. Early studies on CHF showed abnormalities in the mucosal barrier and increased permeability in the small and large intestines, suggesting a particular involvement of intestinal barrier function. However, whether vascular or intestinal dysfunction is the initiating factor in these processes remains debatable. Over the past few years, Sandek et al. have significantly contributed to this field by reporting decreased intestinal blood flow, increased gastrointestinal symptoms, elevated serum LPS levels, and heightened anti-LPS IgA levels in several studies involving patients with chronic HF [56, 64–67]. Of particular interest is the observation that increased intestinal permeability was related to higher right atrial pressure and levels of inflammatory markers in the blood [38, 68].

Epigenetic modifications induced by the GM and its impact on HF

Recent research increasingly highlights the role of epigenetic mechanisms—like DNA methylation, histone modification, and regulation of non-coding RNAs—in CVD progression, including HF [69].

Structural and functional remodeling of the myocardium, characteristic of HF, is a complex process that significantly impacts cardiac function and overall health. This remodeling often involves a series of genomic and

transcriptional changes in cardiomyocytes and adjacent cells, contributing to the onset and progression of the disease. In particular, the accumulation of DNA methylation errors and dysregulation of histone modifications can alter key pathways involved in cardiac health, such as mitochondrial function, oxidative stress responses, and inflammation [70].

External factors can influence these mechanisms, and there is growing evidence that GM and its derived metabolites/toxins can influence not only metabolic and inflammatory responses but also have a direct impact on gene regulation through epigenetic mechanisms [71].

TMAO, SCFAs, and secondary bile acids are among the most characterized GM-derived metabolites/toxins that have been linked to epigenetic regulation in CVDs.

Although more research is needed to clarify the connection between GM, epigenetics, and HF, current evidence suggests a strong link. The composition of GM and the function of epigenetics are intertwined and directly associated with obesity, body weight, and metabolism regulation, all of which are key factors in the development and progression of HF.

Table 3 provides a summary of the function of GM-derived metabolites and their roles on heart health.

SCFAs

SCFAs, produced from the fermentation of dietary fiber, have shown a significant positive impact on the heart, probably due to their anti-inflammatory properties. They are fatty acids with a carbon chain of up to six atoms, and the most relevant are acetate (60% of total SCAFs), propionate (20%), and butyrate (20%) [72]. They play a multifaceted role by suppressing reactive oxygen species, restoring mitochondrial function, and ameliorating cardiac inflammation [73]. They also help regulate blood pressure by acting as vasodilators and modulating the renin-angiotensin system [74]. Additionally, SCFAs serve as an efficient energy source, with their oxidation potentially surpassing that of ketones in failing hearts [75]. Despite these benefits, the exact molecular mechanisms of SCFAs' actions remain partially understood and require further research. Recent studies on patients with severe chronic HF have highlighted a decrease in SCFA-producing bacteria, such as those from the *Eubacterium*, *Faecalibacterium*, *Ruminococcus*, and *Butyricicoccus* genera [76]. This decline correlates with lower plasma levels of SCFAs such as acetate, propionate, and butyrate, which are the most abundant gut-derived SCFAs [73, 77]. Moreover, restoring GM composition by increasing the abundance of beneficial bacteria and SCFAs while reducing harmful bacteria can lead to improvements in clinical

Table 3 Function and role of GM-derived metabolites on HF

Metabolite	Mechanism of action	Effect on HF	Refs
SCFAs	Anti-inflammatory properties	Reduced SCFA levels linked to HF progression	[71–86]
	ROS suppression	Potential reduction in cardiac hypertrophy and fibrosis through HDAC inhibition	
	Restoration of mitochondrial function	May enhance cardiac function via improved glucose metabolism and lipid regulation	
	Regulation of blood pressure (vasodilation, modulation of renin-angiotensin system)		
	Energy source for the heart		
	HDAC inhibition		
	Modulation of TET enzymes		
TMAO	Activates Smad3 signaling pathways	TMAO levels increased in chronic HF patients, linked to HF progression	[87–99]
	Increases pro-inflammatory cytokines (e.g., via NF-κB pathway)	Predictive marker for HF severity and poor prognosis	
	Induces mitochondrial ROS accumulation by inhibiting SIRT3 and SOD2	Associated with myocardial hypertrophy and fibrosis	
	Modifies DNA methylation (affects methyl-donor availability)	Disrupts cardiac energy metabolism and mitochondrial function	
	Chromatin remodeling (e.g., H3K4me3 upregulation)		
Bile Acids	Regulates lipid and glucose metabolism (e.g., through FXR, TGR5)	Increased secondary-to-primary BA ratio in HF	[76, 100–107]
	Modulates mitochondrial function	Linked to atrial fibrillation in HF patients	
	Regulates inflammation (e.g., via pro- and anti-inflammatory pathways)	Dysregulated BA signaling may impair lipid and energy metabolism with effect on cardiac stress	

parameters and inflammation levels 12 months after a first episode of HF [78].

SCFAs are considered important inhibitors of host histone deacetylases (HDACs), which remove histone lysine acetyl groups, leading to chromatin condensation and transcriptional silencing [73]. SCFAs can also modulate the activity of ten-eleven translocation methylcytosine dioxygenase (TET) enzymes, which play a key role in DNA demethylation [71].

Recent studies have demonstrated that HDAC activities play a role in regulating the heart's hypertrophic response: studies conducted in animal models showed that HDAC inhibition reduces cardiac hypertrophy and fibrosis by acetylation and deacetylation of target genes [79, 80]. Butyrate exerts protective effects by altering histone H3 modification, which affects G1-specific cell cycle proteins, leading to the arrest of smooth muscle cell proliferation. Furthermore, butyrate has been found to enhance cardiac function in diabetic mice by inhibiting HDAC, leading to increased glucose uptake through GLUT1 and GLUT4 activation, as well as improving serum cholesterol levels and heart function [81, 82]. Additionally, oral administration of sodium butyrate in rats subjected to myocardial infarction reduced HDAC activities that resulted in cardiac dysfunction attenuation [83] and attenuated cardiac hypertrophy and fibrosis in several animal models of CVDs [81, 82, 84]. Valproic acid, another SCFA with HDAC inhibitory activity, has similarly been shown to improve cardiac function [85]. These findings indicate that SCFAs with HDAC inhibitory activity, such as butyrate, may be safe and effective in humans and exert a cardioprotective effect. Therefore, the reduced plasma levels of SCFAs observed in HF patients may contribute to the worsening of cardiovascular outcomes. However, caution is advised since the high concentrations required for HDAC inhibition could lead to off-target effects, limiting their therapeutic application in CVDs [86].

TMAO

The GM plays a crucial role in converting dietary choline into TMA, which is absorbed into the bloodstream and then oxidized to TMAO in the liver. Several intestinal bacterial strains, such as Firmicutes and Proteobacteria, can produce TMA. In patients with HF, as discussed above, there is an increased prevalence of these bacterial strains [87, 88], suggesting that alterations in the intestinal microbiota of HF patients may influence the levels of TMAO by modulating TMA synthesis within the intestines. Moreover, several studies have demonstrated that TMAO levels were higher in chronic HF patients when compared with healthy controls, with strong associations between TMAO and disease severity (NYHA classes) and poor prognosis (death, HF hospitalization, composite [89, 90]. In line with this, TMAO has been implicated in advancing HF and is considered a potent prognostic marker for HF [87].

The ways by which TMAO affects heart function are several. TMAO can directly influence myocardial hypertrophy and fibrosis by activating the Smad3 signaling pathway [91, 92]. Mice fed with TMAO exhibit worsening cardiac conditions, including cardiac fibrosis, pulmonary edema, left ventricular dilation, and elevated brain natriuretic peptide levels [93]. Additionally, TMAO directly induces an inflammatory response by activating inflammatory pathways such as NF-κB and increasing the expression of pro-inflammatory cytokines and chemokines [94]. Moreover, mitochondrial reactive oxygen species (mtROS) accumulation could also be promoted by TMAO by inhibiting sirtuin 3 (SIRT3) and superoxide dismutase 2 (SOD2); this in turn activates NLRP3 inflammasomes, causing endothelial inflammation [95, 96]. The impact of TMAO on mitochondrial function is also significant. Long-term TMAO exposure affects cardiac energy metabolism and mitochondrial function by disrupting pyruvate and fatty acid oxidation, contributing to ventricular remodeling and the development of HF [97].

At the epigenetic level, GM's utilization of choline can influence DNA methylation patterns across multiple tissues in adult mice. This was demonstrated in a gnotobiotic mouse model, where choline consumption by gut bacteria led to changes in DNA methylation profiles in various organs, including the brain, heart, liver, and colon. DNA methylation reactions are highly dependent on a constant supply of methyl-donor precursors, such as choline, folate, and betaine, which are obtained through the diet. The competition between gut bacteria and host cells for these methyl donors can result in a global reduction in DNA methylation levels across these organs that lead to hypermethylation or hypomethylation of genes involved in inflammation, lipid metabolism, and oxidative stress, potentially contributing to the pathogenesis of CVD like atherosclerosis and HF [98]. Recently, it was also suggested that TMAO can extensively remodel chromatin in endothelial cells through upregulation in H3K4me3 and other H3 histone methylation [99].

Bile acids

Bile acids (BAs) are another class of gut-derived molecules that play a key role in human physiology, acting as important signaling molecules. Primary BAs are synthesized from cholesterol in the liver, conjugated, and secreted into the bile, which is then released into the small intestine to facilitate the absorption of dietary

lipids and fat-soluble vitamins. In the gut, microorganisms further transform these conjugated primary BAs through deconjugation and other metabolic processes, generating a pool of secondary BAs with distinct physiological properties, thus further increasing the diversity of the BAs pool [100]. Over the past 20 years, BAs have been recognized for facilitating inter-tissue communication, starting in the liver, where they are produced, moving through the intestine, where they are altered by the GM, and impacting multiple organs. Their chemical diversity, largely influenced by GM, allows for precise modulation of the body's adaptive responses [101]. In HF patients, reduced cardiac output leads to decreased blood flow to the liver and congestion, which negatively affects liver function and BA excretion. This can further disrupt both gut and liver circulation, raising BA levels. Specifically, a recent study by Mayerhofer and colleagues found an elevated ratio of secondary-to-primary BAs in HF patients respect to controls, pointing to BA metabolism, rather than just BA levels, as being central to chronic HF. Moreover, the ratio has been consistently associated with increased mortality risk in HF patients [102]. Additionally, another study observed that elevated concentrations of hydrophobic BAs were predictive of atrial fibrillation in a cohort of 250 HF patients [103]. On the other hand, high total serum BA levels have been linked to liver-related heart dysfunction in mouse models, likely through impaired oxidation of cardiac fatty acids. This implies that the overall BA pool, rather than specific BA types, may influence HF [104, 105].

BAs have garnered significant attention for their potential to modulate cardiac function through diverse mechanisms, including regulation of lipid and glucose homeostasis, mitochondrial function, and inflammatory pathways [76]. Under normal conditions, BAs are involved in lipid and glucose metabolism via the activation of receptors such as Farnesoid X-activated receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5), which help to maintain metabolic homeostasis. However, dysregulated BA signaling can impair lipid metabolism, resulting in increased triglycerides and cholesterol levels, with profound effects on several physiological pathways, such as cardiac stress [106]. Moreover, BAs can modulate mitochondrial function, with excess or altered secondary BAs potentially leading to mitochondrial stress and dysfunction. This can result in reduced energy and increased oxidative stress, which can impair cardiac function. Besides, BAs have pro- and anti-inflammatory properties; for example, some secondary BAs, when in high levels, can activate pro-inflammatory pathways, with potential impact on systemic inflammation and heart damage [107].

GM, epigenetic, and HF in the elderly

Similar to other age-related conditions, the higher occurrence of HF among older adults correlates significantly with a state of chronic inflammation [108]. This chronic, sterile, and low-grade inflammation is named inflammaging, which is associated with an increased risk of chronic diseases, disability, frailty, and premature death [109]. Thus, inflammaging has also been closely linked to gut dysbiosis in the elderly [110–112]. The microbiome formation at birth is determined by the delivery mode and is impacted by the feeding method as infants grow. The microbiome evolves with age during adulthood, influenced by dietary preferences, genetic factors, emotional well-being, lifestyle habits, and environmental conditions [113]. As individuals grow older, their GM tends to lose diversity, which can lead to dysbiosis [114]. This dysbiosis, as discussed above, leads to increased gut permeability, allowing microbial metabolites and pro-inflammatory molecules to enter the circulation, thus exacerbating inflammaging in the elderly.

Simultaneously, aging is also associated with epigenetic alterations, such as DNA methylation, histone modifications, chromatin remodeling, and RNA modification. These epigenetic changes can significantly impact the expression of genes involved in inflammatory pathways, leading to a sustained inflammatory response commonly seen in the elderly. Moreover, the chronic inflammation characteristic of inflammaging can further exacerbate epigenetic alterations, creating a vicious cycle [115]. Elevated inflammatory markers can drive changes in DNA methylation patterns and histone modifications, reinforcing the inflammatory state and potentially leading to the development of age-related diseases, including HF.

Given the bidirectional relationship between the GM and host epigenetics described above, the interplay between these systems becomes particularly relevant in aging, as they may exacerbate the risk and progression of HF in elderly populations (Fig. 1).

Gut dysbiosis and HF in the elderly

The GM of adult humans consists predominantly of permanent and transitory bacterial species from 17 different phyla, including Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, which co-evolved with the host to regulate normal gut functions [116, 117].

Findings across different species indicate that a decline in intestinal barrier function with age is a common characteristic of the aging process. Besides, it is becoming increasingly evident from these studies that a weakened intestinal barrier in aging organisms is closely associated with a decline in systemic health [118].

Despite the lack of complete understanding regarding how GM dysbiosis contributes to cardiovascular

disorders, it is suggested that as people age, their intestinal permeability rises, leading to increased diffusion of harmful bacterial by-products that fuel ongoing inflammation [119].

For example, it has been shown that healthy young adults and elderly individuals exhibited similar small intestinal, colonic, and whole gut permeability. Of note, among individuals with irritable bowel syndrome (IBS), with mild disturbances in gastrointestinal health, small intestinal and whole gut permeability were higher in the elderly group than in young adults, particularly in those with IBS-diarrhea subtype [120]. This suggests that aging may be a significant risk factor for compromised intestinal barrier function, especially in individuals with pre-existing gastrointestinal conditions.

Although it is not yet known whether microbiota alterations are a cause or consequence of aging, many studies have demonstrated changes in the microbiota with increasing age (Table 4). For instance, Jeffery et al. demonstrated that advancing age is accompanied by significant changes in GM, characterized by an increase in pro-inflammatory symbionts and a decrease in beneficial microorganisms [121]. However, the impact of aging on GM composition is complex and sometimes contradictory. Although some studies did not find significant differences in microbiota composition between healthy young and aged adults [122], recent genome-wide association studies (GWAS) have shown that GM changes can be predictive of the human host's age [123]. Indeed, a growing body of research indicated that, compared to adults, elderly people exhibit a decline in beneficial gut bacteria and a shift toward a higher proportion of pro-inflammatory bacteria [123, 124]. This age-related dysbiosis includes a decrease in beneficial bacteria such as *Lactobacillum, Bifidobacterium,* and some members of Firmicutes with anti-inflammatory properties and an enrichment in opportunistic pathogens such as Bacteroidetes and Proteobacteria, which can stimulate the inflammasome pathway in the intestine, leading to an inflammatory response [125–127]. The importance of GM in aging is further corroborated by recent research on centenarians from various regions. These studies suggest that centenarians possess a unique microbiota profile associated with longevity, characterized by increased

Table 4 Key studies highlighting changes in GM composition in older adults

Author [ref]	Study Population	Molecular technique	Microbiota profile
Jeffery et al. [121]	Older subjects (aged 65 +)	Bacterial 16S rRNA gene sequencing	↓ beneficial microorganisms ↑ pro-inflammatory symbionts
Bian et al. [122]	Healthy aged (aged 60–79) *vs* healthy centenarians (aged 94 +) *vs* younger adults (aged 30–50)	Bacterial 16S rRNA gene sequencing	No significant differences
Galkin et al. [123]	Three age groups (20–39, 40–59, and 60–90 years)	Genome-wide association studies (GWAS)	GM changes predictive of the human host's age
Leite et al. [124]	Older subject (aged 66–80) *vs* young (aged 18–35)	Bacterial 16S rRNA gene sequencing	↓ microbial diversity; Bacteroidetes ↑ Proteobacteria (*Escherichia* and *Klebsiella)*
Biagi et al. [128]	Healthy semi-supercentenarians (aged 105 +) *vs* young adults (aged 22–48)	Bacterial 16S rRNA gene sequencing	↓ *Coprococcus*, *Roseburia*, and *Faecalibacterium*, belonging to the *Lachnospiraceae* and *Ruminococcaceae* families ↑ *Oscillospira*, *Odoribacter*, *Butyricimonas, Eggerthella*, *Akkermansia*, *Anaerotruncus*, *Synergistaceae*, *Bilophila*, and *Christensenellaceae*
Kong et al. [129]	Healthy centenarians (aged 90 +) *vs* young adults (aged 24–64)	Bacterial 16S rRNA gene sequencing	Increased longevity associated with increased taxonomic alpha diversity
Wu et al. [130]	Healthy centenarians (aged 99 +) *vs* Young (aged 21–33) and Older (68–88) subjects	Shotgun metagenomic sequencing	↓ *Faecalibacterium*, *Eubacterium*, *Coprococcus*, *Dorea*, and *Ruminococcus*, ↑ *Bifidobacterium*, *Methanobrevibacter*, *Pyramidobacter*, *Escherichia*, and *Synergistes*
Zhang et la. [132]	Elderly HF patients (aged 70 +) *vs* age-matched controls	Bacterial 16S rRNA gene sequencing	↓ Firmicutes ↑ Bacteroidetes
Kamo et al. [133]	Elderly HF patients (aged 60–90) *vs* Young HF patients (aged 30–60)	Bacterial 16S rRNA gene sequencing	↓ Bacteroidetes, *Faecalibacterium, F. prausnitzii,* and *Clostridium clostridioforme* ↑ Proteobacteria, *Lactobacillus, and L. salivarius*
Peng et al. [134]	Elderly HF patients (aged 65 +) with sarcopenia *vs* without sarcopenia	Bacterial 16S rRNA gene sequencing	↓ *Nocardiaceae*, *Pseudonocardiaceae*, Alphaproteobacteria, and *Slackia* ↑ *Synergistetes*

microbial diversity and enrichment of beneficial bacteria such as *Oscillospira*, *Christensenellaceae*, *Akkermansia*, and *Bifidobacterium* [2, 128, 129]. Another study found that centenarians in Sardinia (Italy) exhibit higher microbial diversity compared to young and old subjects. Specifically, their microbiome showed a decline in genera such as *Faecalibacterium*, *Eubacterium*, *Coprococcus*, *Dorea*, and *Ruminococcus*, alongside an increase in other beneficial genera like *Bifidobacterium*, *Escherichia*, and *Synergistes*. Despite a reduced expression of carbohydrate degradation genes, these centenarians maintained a high capacity to produce SCFAs, which support epithelial barrier function, beneficial microbial growth, and immune regulation while reducing pathogen colonization [130]. This unique GM composition in centenarians could contribute to their exceptional health and longevity, highlighting the potential role of a balanced and diverse GM in promoting healthy aging.

Despite the large body of work demonstrating a close relationship between GM alteration and HF in adults reported above, there is a paucity of information about how aging and age-related dysbiosis could specifically affect this phenomenon. Indeed, it could be assumed that the aging process may contribute to HF development, not only through its detrimental effect on cardiovascular structure and function but also as a consequence of the age-related alteration of the composition and diversity of the GM [4]. Unexpectedly, only a few studies have specifically examined the connection between GM and HF in aged subjects and if age-related dysbiosis per se has an impact on this relationship.

Wang and colleagues were delving into the relationships between the gut microbiome, host age, metabolism, and their implications for long-term cardiovascular disease risk. Their research focused on examining the gut microbiome patterns related to age and metabolism and establishing a microbial age scale using 55 age-specific bacteria from a healthy multimorbidity group. To describe the range of metabolic disturbances, they initially developed five distinct clusters of metabolic multimorbidity in a cohort of 10,207 Chinese participants. MC1, the first cluster identified, exhibits metabolic healthiness. MC2 has low amounts of high-density lipoprotein cholesterol, while MC3 has elevated levels of low-density lipoprotein cholesterol. MC4 displays signs associated with obesity, while MC5 is distinguished by high blood sugar levels. The incident CVD risk during an 11.1-year follow-up was 75% higher for MC4 and 117% higher for MC5 than for MC1. In individuals aged 60 and above in MC4 and MC5, a high microbial age worsened the risk of cardiovascular disease linked to MC4 and MC5. Conversely, a low microbial age, marked by a decreased presence of *Prevotella copri*, effectively mitigated the CVD risk associated with MC4 and MC5, regardless of age, gender, education, lifestyle, diet, and medication use. Even among older adults with unhealthy metabolism, the association between microbial age and reduced risk of cardiovascular disease persists, suggesting a regulating role of microbial age in the cardiovascular health of this population [131].

As observed in adult HF populations, elderly patients (over 70 years of age) also exhibit alterations in GM compared to age-matched controls. Recently, it was found that elderly chronic HF patients present a significantly different gut flora compared to control subjects despite having similar risk factors for CHF (such as coronary artery disease and hypertension). Specifically, the authors identified a statistically significant reduction in Firmicutes and an increase in Bacteroidetes abundance in the chronic HF group. Moreover, the more severe the level of HF, the lower the diversity of GM species in these patients. Additionally, the analysis of plasma levels of Phenylacetylglutamine (PAGln), a by-product of the catabolism of the essential amino acid phenylalanine by intestinal microorganisms, showed an increase in the chronic HF group compared to controls, with levels further rising as HF severity worsens. These findings suggest that the normal function of the intestinal flora is impaired in HF and that pathophysiological changes in the gut may, in turn, exacerbate the progression of HF [132].

Similarly, Kamo et al., observed differences in GM communities of elderly HF patients with respect to age-matched healthy control. Additionally, they also found that older HF patients tended to harbor more Proteobacteria but less Bacteroidetes compared to their younger HF counterparts. A depletion of the genus *Faecalibacterium* and an enrichment of *Lactobacillus* was also observed in the GM of older HF patients. These findings suggest that the alteration of the GM observed in HF patients varies further with age [133].

The presence of comorbidities further worsens the condition in older patients. For instance, a recent study observed that HF patients with and without sarcopenia differ in terms of intestinal microbial composition. In this study, the authors observed a significant difference in the overall structure and diversity of microbial communities between control individuals and those with HF, regardless of sarcopenia status, with no variance noted between HF patients with and without sarcopenia. *Nocardiaceae*, *Pseudonocardiaceae*, Alphaproteobacteria, and *Slackia* were significantly enriched in HF patients without sarcopenia, whereas *Synergistetes* were more abundant in HF patients with sarcopenia [134].

GM-mediated epigenetic alterations in age-related HF

The aging process is marked by a multitude of physiological changes, including a decline in the precision of epigenetic regulation, leading to aberrant gene expression patterns. Epigenetic changes are recognized as hallmarks of aging and are closely linked to the onset and progression of age-related diseases, including HF [20, 22, 135]. However, the exact role of these changes in cardiac aging remains only partially understood. While it is well established that epigenetic alterations contribute to HF, it remains unclear which epigenetic changes are primary drivers of the pathology and which are secondary consequences of the aging process. Elderly individuals, who are at the greatest risk for developing HF, display distinct epigenetic profiles compared to younger counterparts [136]. These age-related shifts in epigenetic regulation could contribute to chronic, long-term modifications in gene expression, which not only reflect the biological aging of the heart but also exacerbate existing vulnerabilities to cardiac dysfunction.

However, most studies on the epigenetic basis of HF have been conducted in young or adult subjects using murine models [137–139] or human left ventricle biopsies [140–142]. This focus on younger populations underscores a critical gap in understanding how aging influences the epigenomic landscape in the context of HF. The lack of studies on the epigenetic alterations in the aging heart limits our ability to fully elucidate the mechanisms that drive age-related HF. Addressing these knowledge gaps is crucial, as the failure to accurately model the epigenetic landscape in elderly populations limits our ability to understand the mechanisms underlying age-related HF.

As a consequence, direct studies on the effects of dysbiosis and GM-derived metabolites on cardiac-epigenetic changes, specifically in elderly individuals, are lacking. However, there is emerging evidence of a relationship between GM and epigenetic modifications in systemic contexts. For instance, recent studies have confirmed that GM bacterial species can modulate a wide range of physiological and biochemical processes and that there exist associations between GM and blood-based epigenetic age acceleration in a heterogenic population of subjects aged between 38 and 84 years [111]. Another study found a causal relationship between the GM and four epigenetic clocks, which can be mediated by several inflammatory factors [143]. These findings suggest that GM can influence age-related epigenetic regulation, though the specific impact of these changes on the cardiac epigenome remains unexplored. Given the absence of studies directly investigating the interplay between the GM and the cardiac epigenome in the elderly, it is likely that the effects observed in systemic contexts, such as blood-based epigenetic clocks, may also extend to the heart. However, without direct evidence, it remains speculative how the dysbiosis commonly observed in the elderly may contribute to epigenetic changes predisposing to HF. Future research that bridges this gap is needed to understand whether GM influences the epigenetic regulation of the heart in aging and how this relationship might contribute to the development and progression of HF in elderly populations.

Conclusions

This review has examined the intricate interplay between the GM, epigenetic modifications, and HF. The observation that the GM in HF patients becomes increasingly altered with the progression of the disease supports the bidirectional relationship described by the gut-heart axis hypothesis, where changes in the heart's function can further disrupt gut homeostasis, perpetuating a cycle of deterioration. At the same time, the administration of probiotics and prebiotics before inducing myocardial alterations in animal models can reduce heart damage, suggesting a cardioprotective effect of these substances. This not only highlights their therapeutic potential but also reinforces that the state of GM significantly impacts the progression of the disease through GM-derived metabolites. However, the molecular mechanisms driving this complex interplay are not yet fully understood and warrant further investigation.

Experimental and clinical studies increasingly recognize epigenetic changes as possible modulators in this relationship. Epigenetic modifications are reversible, offering potential therapeutic targets. They provide a mechanism through which metabolites produced by the GM can durably and reversibly influence gene expression in cardiac cells. This implies that even small changes in the gut environment can have long-term effects on cardiac function. However, the ability of GM-derived metabolites to influence gene regulation through DNA methylation and histone modifications introduces a new layer of complexity to our understanding of HF, posing several difficulties.

These challenges lie in the multifactorial nature of the connection between gut bacteria and the host, which can involve various biological processes, with epigenomics being just one among many. This complexity makes it difficult to investigate the specific contributions of epigenetic mechanisms in the context of HF.

Additionally, the limited availability of myocardial tissue from living patients restricts direct study of epigenetic alterations in individuals with heart disease. As a result, most current research relies on animal models, which may not fully replicate the intricate dynamics of human GM and its interactions with HF. In these

models, HF is often induced through surgical techniques (*i.e.* coronary artery ligation), genetic modifications, and pharmacological approaches, further limiting the ability to translate findings to human conditions.

Moreover, both epigenetics and GM change over time, influenced by diet, lifestyle, sex, and aging. Aging is characterized by a state of sterile and low-grade inflammation, named inflammaging which drives multiple pathological conditions. In elderly individuals, the epigenetic landscape differs significantly from that of younger or adult subjects due to age-related changes. Concurrently, the GM undergoes significant alterations. This complex interplay of aging-related epigenetic changes and microbiome alterations in the elderly renders it impossible to directly translate findings from younger populations to the elderly. Indeed, these age-related epigenetic modifications serve as a fundamental background upon which other factors, such as the altered microbiome, act, influencing the development and progression of diseases like HF. Therefore, studying how epigenetic mechanisms in the elderly influence the onset and progression of HF requires a specific approach, especially when combined with the impact of stressors such as dysbiosis and the metabolites produced by an altered GM.

Furthermore, sex also plays a significant role in this scenario. Previous research has demonstrated that GM may play a role in the differing rates of metabolic disorders observed between males and females, as well as a sex-specific influence on how diet affects GM composition [144]. Indeed, men and women produce different microbiota-derived metabolites due to variations in gut composition and host metabolism. For instance, SCFAs levels, such as butyrate and propionate, may differ and influence sex-specific inflammation responses. These microbial metabolites can modulate hormone pathways differently by sex, impacting conditions like obesity, cardiovascular and mental health, and they also can influence DNA methylation and histone modification, possibly affecting longevity and disease susceptibility differently in men and women [145, 146]. These interactions suggest that both personalized and age-appropriate approaches to health interventions could improve outcomes in gender- and age-specific health challenges [147, 148].

However, how to relate sex to the involvement of GM in HF onset and progression, mediated by epigenetic modifications, is an area that requires further investigations.

Bridging these gaps is crucial for developing personalized therapies to prevent and treat HF, ultimately improving prognosis and patient outcomes, especially among the elderly, where the burden of the disease is most pronounced. By identifying specific metabolite-induced epigenetic modifications, we can tailor treatments to individual patients based on their unique microbial profiles and epigenetic signatures. A multidisciplinary approach, integrating expertise from microbiology, genetics, and cardiology, is necessary to unravel the complexities of this relationship.

In conclusion, investigating the epigenetic effects of GM-derived metabolites on HF, especially in the elderly population, is crucial for several reasons. It can help us better understand the pathogenesis of age-related heart disease, identify new biomarkers and therapeutic targets, and ultimately improve the outcome of older adults with HF. Moreover, the study of epigenetic mechanisms can lead to the identification of new biomarkers for the early diagnosis and prognosis of HF. Additionally, these mechanisms could represent new therapeutic targets for developing drugs capable of modulating gene expression and improving cardiac function.

Future directions

Future studies are needed to better understand the complex interplay between GM, epigenetic modifications, and HF.

First, longitudinal studies will be essential to elucidate the dynamic relationship between GM, epigenetic changes, and HF progression over time, which cross-sectional or short-term studies may fail to capture. Longitudinal research is also crucial for evaluating potential therapeutic interventions' safety, efficacy, and long-term effects, as it can uncover delayed or cumulative adverse effects that might be overlooked in shorter studies. In addition, comprehensive outcomes should encompass not only alterations in the GM but also broader indicators of healthspan—including physical and cognitive function—as well as lifespan. Such holistic metrics can provide insights into how treatments may impact quality of life, functional capacity, and survival, offering a more thorough assessment of therapeutic value beyond merely extending life expectancy.

Moreover, mechanistic studies will be crucial to understand the precise molecular pathways by which GM influences epigenetic modifications and uncover the mechanisms underlying aging and disease progression. A longitudinal approach that assesses both microbiome and epigenome profiles at baseline and several follow-up points in a diverse population—from young to older adults—under various therapeutic interventions or dietary regimens could illuminate critical mechanisms linked to physical and cognitive decline, as well as the early onset of age-related diseases. Such studies may also identify specific microbiome-epigenome signatures that predict health outcomes or treatment responses, providing a foundation for more targeted therapeutic strategies.

However, to establish causality, experimental models in cells and mice are essential. These models allow for controlled manipulation of environmental factors, GM, and epigenetic pathways to directly observe the impact on healthspan, lifespan, and susceptibility to concomitant diseases. Integrating findings from both human and experimental models could ultimately lead to precision approaches that modify GM to support healthy aging and mitigate disease risk.

Additionally, clinical trials are needed to evaluate the efficacy of dietary interventions, probiotics, and prebiotics in modifying GM composition and improving HF outcomes. As previously mentioned, experimental approaches designed to compare the most effective and translational dietary or pharmacological interventions could help identify the best options for different age groups. In recent years, numerous epigenetic modulators have emerged, highlighting new avenues for targeted therapies. Combining dietary interventions with these epigenetic modulators may offer a synergistic approach to shift the epigenome in a way that reduces gut dysbiosis and promotes overall health. This integrated strategy has the potential to yield tailored treatments that address both microbiome and epigenetic factors, optimizing outcomes for individuals with HF.

Information derived from all these studies will be propaedeutic to develop personalized interventions based on individual microbiota profiles and epigenetic markers that hold promise for creating more effective treatment strategies for HF, although this goal is highly ambitious and among the most critical in advancing HF care, assessing its effectiveness presents significant challenges. Evaluating the accuracy of any personalized approach can be hampered by biases arising from small sample sizes. Therefore, it is crucial to identify subgroups of patients with similar microbiome and epigenetic characteristics, enabling treatment of patient clusters with shared features. This approach would allow for a more accurate assessment of treatment efficacy, reducing bias and increasing the reliability of results in measuring the success of personalized interventions.

Abbreviations

BAs	Bile acids
CHD	Coronary heart disease
CVD	Cardiovascular diseases
FXR	Farnesoid X-activated receptor
GM	Gut microbiota
GWAS	Genome-wide association studies
HDACs	Histone deacetylases
HF	Heat failure
IL	Interleukin
LPS	Lipopolysaccharide
LVEF	Left ventricular ejection fraction
PAGln	Phenylacetylglutamine
SCFAs	Short-chain fatty acids
SIRT3	Sirtuin 3
SOD2	Superoxide dismutase 2
TGR5	G-protein-coupled bile acid receptor 1
TJP	Tight junction
TMAO	Trimethylamine N-oxide
TNF	Tumor necrosis factor

Author contributions

SM contributed to the review's conception and design. SM, GM, FP, and LP performed article acquisition and interpretation. SM, GM, FP, LP, and YR wrote the original draft. SM generated the figure. All authors have approved the submitted version of the manuscript. All authors agreed to be personally accountable for their contributions and to ensure the accuracy and integrity of any part of the work.

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Availability of data and materials

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Declarations

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Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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