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Unveiling the relationship between gut microbiota and heart failure: Recent understandings and insights

Hritvik Jain, MBBS [a,*], Mohammed Dheyaa Marsool Marsool, MBChB [b], Aman Goyal, MBBS [c], Samia Aziz Sulaiman, MD [d], Laveeza Fatima, MBBS [e], Muhammad Idrees, MBBS [f], Bhavya Sharma, MBBS [g], Vamsikalyan Borra, MBBS [h], Prakash Gupta, MD [i], Abdullah Nadeem, MBBS [j], Jyoti Jain, MBBS [a], Hassam Ali, MD [k], Amir H Sohail, MD [l]

[a] Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India
[b] Department of Internal Medicine, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq
[c] Department of Internal Medicine, Seth GS Medical College and KEM Hospital, Mumbai, India
[d] School of Medicine, University of Jordan, Amman, Jordan
[e] Allama Iqbal Medical College, Lahore, Pakistan
[f] Lahore General Hospital, Lahore, Pakistan
[g] Department of Internal Medicine, Baroda Medical College and SSG Hospital, Vadodara, India
[h] Department of Internal Medicine, University of Texas Rio Grande Valley, TX, United States
[i] Virgen Milagrosa University Foundation College of Medicine, San Carlos City, Philippines
[j] Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan
[k] Department of Gastroenterology, East Carolina University, North Carolina, United States
[l] Department of Surgery, University of New Mexico Health Sciences Center, Albuquerque, NM, United States

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ABSTRACT

Gut microbiota, which comprises a broad range of bacteria inhabiting the human intestines, plays a crucial role in establishing a mutually beneficial relationship with the host body. Dysbiosis refers to the perturbations in the composition or functioning of the microbial community, which can result in a shift from a balanced microbiota to an impaired state. This alteration has the potential to contribute to the development of chronic systemic inflammation. Heart failure (HF) is a largely prevalent clinical condition that has been demonstrated to have variations in the gut microbiome, indicating a potential active involvement in the pathogenesis and advancement of the disease. The exploration of the complex interplay between the gut microbiome and HF presents a potential avenue for the discovery of innovative biomarkers, preventive measures, and therapeutic targets. This review aims to investigate the impact of gut bacteria on HF.

Introduction

The gut microbiota, an assembly of countless microorganisms residing in the human intestines, establishes a mutually beneficial relationship with the human body.[1] This symbiotic interaction profoundly influences various aspects of human health, including metabolism, immune responses, and secretions.[1] Similarly, the gut environment reciprocally influences the growth and functions of

* Corresponding author.
E-mail address: hritvikjain2001@gmail.com (H. Jain).

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these microorganisms.[1] The human intestinal microbiota forms an essential ecosystem, comprising a diverse array of bacteria, archaea, viruses, protozoa, and fungi. A healthy microbiota mainly consists of four primary categories of bacteria: Actinobacteria, Firmicutes, Proteobacteria, and Bacteroides. These microbial groups dynamically adapt to shifts in human lifestyle.[2]

Dysbiosis, marked by a disruption in microbial composition or activity, upsets the symbiotic equilibrium between the gut microbiota and the host. This disruption is influenced by host-specific factors such as genetic makeup, health status (including infections and inflammation), and lifestyle choices, as well as environmental factors like diet (high sugar, low fibre), hygiene, and xenobiotics (antibiotics, drugs, food additives).[3] Dysbiosis involves a transition from a healthy gut flora to a dysfunctional array of organisms, promoting disease states. Changes in gut microbiota profoundly affect various inflammatory pathways, particularly in older adults, potentially contributing to chronic systemic inflammation.[4]

Heart failure (HF) is a multifaceted clinical condition characterized by diverse causes and underlying physiological mechanisms. It has a significant global impact, affecting more than 64 million individuals, and its prevalence is swiftly increasing, particularly among the elderly in affluent nations.[5] HF manifests as a syndrome with specific symptoms and indicators resulting from impaired cardiac function, ultimately leading to reduced life expectancy. The European Society of Cardiology guidelines stress the importance of specific symptoms and signs (Tables 1 and 2), objective evidence of cardiac dysfunction, preferably through echocardiography, and, if uncertainties persist, a positive response to targeted HF treatment to confirm a diagnosis.[6] HF can present either as an acute or chronic form. The acute form of HF is associated with various inflammatory markers, while the chronic form is characterized by an abnormal inflammatory state involving pro-inflammatory agents that are considered pivotal in the development of HF.[7]

Gut dysbiosis, encompasses changes in the composition and functionality of the gut microbiota, disrupting the gastrointestinal tract balance. This disruption can stem from various factors like diet, antibiotic usage, stress, or infections.[8,9] One crucial aspect of precision medicine in HF is the gut microbiome. Preliminary clinical research has uncovered similar disruptions in the gut microbiome among individuals with HF, and studies have provided proof of the gut microbiome playing an active role in HF development and underlying mechanisms.[10–12] A thorough understanding of how the gut microbiome interacts with the host in individuals with HF holds the potential to unveil new biomarkers for the disease, identify targets for prevention and treatment, and enhance the categorization of disease risk. Moreover, the involvement of gut dysbiosis, caused by a multitude of factors, including nutrition, inflammation, stress, and antibiotic use, with metabolic syndrome, which is a series of metabolic disorders such as insulin resistance, glucose intolerance, central obesity, dyslipidemia, and hypertension, is also crucial in understanding the intricacies between the gut microbiota and heart failure, since metabolic syndrome is a well-established known factor of cardiovascular disease, particularly heart failure, as shown in Fig. 1.

This current review emphasizes recent advancements in understanding the role of gut microbiota in heart failure development and associated severe cardiovascular disease (CVD) complications. This article delves into strategies to target the gut microbiota for potential HF prevention and treatment. Additionally, it explores the influence of gut microbiota on HF and potential corresponding interventions.

Key microorganisms composing gut microbiota

The gut microbiome is dynamic and constantly evolving and consists of a multitude of bacteria from many taxonomic classifications. The primary phyla observed in the human gut are Bacteroides and Firmicutes, while there are also smaller contributions from other taxa such as Proteobacteria, Actinobacteria, and Verrucomicrobia.[13] Within these taxonomic groups, a diverse array of genera and species fulfill distinct functions in the maintenance of gastrointestinal equilibrium.

Bacteroides, a prominent microbial group inside the gut, is recognized for its significant role in the breakdown of complex carbohydrates and the synthesis of vital metabolites such as short-chain fatty acids (SCFAs), notably butyrate.[9] The Firmicutes phylum has a diverse array of activities, wherein specific individuals exhibit specialization in the process of fermenting dietary fiber and producing SCFAs.[9] The genus *Prevotella*, which is commonly linked to plant-based diets, plays a significant role in the metabolism of carbohydrates. In contrast, Proteobacteria, such *as Escherichia coli*, have been observed to induce inflammation when their population is increased.[14] *Akkermansia muciniphila* is acknowledged for its involvement in the breakdown of mucin and the maintenance of intestinal barrier integrity.

Risk factors associated with gut dysbiosis

The makeup of the microbiota is influenced by selection forces exerted by the host and the environment. Numerous elements have been found as influential in shaping, structuring, and diversifying.[15,16] For example, the Western diet alters gut-barrier permeability by decreasing Bacteroidetes and other gut barrier-promoting bacteria.[15] Also, there have been reports linking obesity to dysbiosis in HF. The gut microbiome of obese mice, which had no leptin satiety factor, showed an alteration in the ratio of Bacteroidetes and

Table 1
European society of cardiology definition of heart failure.

Criteria	Description
I. Symptoms of heart failure	Symptoms present at rest or during exercise
II. Objective evidence	Objective evidence of cardiac dysfunction, preferably confirmed by echocardiography, at rest
III. Response to treatment	Favorable response to treatment specifically directed towards heart failure, in cases where diagnosis is unclear

Table 2
Heart failure - symptoms and signs.

Symptoms	Signs
Dyspnea (on exertion, nocturnal)	Edema, ascites
Reduced exercise tolerance	Elevated jugular venous pressure
Fatigue, lethargy	Crepitations or wheeze
Orthopnea	Tachycardia
Nocturnal cough	Third heart sound, murmurs
Wheeze	Hepatomegaly
Anorexia	Displaced apex beat
Confusion/delirium (elderly)	Cachexia and muscle wasting

Firmicutes, similar to humans.[16,17] The use of antibiotics also plays a significant role in the occurrence of gut dysbiosis by disrupting the mechanism of competitive exclusion, which is a fundamental characteristic through which the microbiota eliminates pathogenic microbes.[17]

Identifying and quantifying techniques in gut biota

Several advanced tools and techniques are employed to quantify and identify gut biota composition accurately (Table 3).[18,19] One of the most common methods is 16S rRNA sequencing, which targets a specific gene found in all bacteria. Metagenomic sequencing takes a broader approach, sequencing all the genetic material in a sample, providing a comprehensive view of the entire gut microbiome, including bacteria, viruses, fungi, and other microorganisms.

The importance of gut microbiota to overall health

Due to its extensive genetic content and metabolic repertoire, the gut microbiota confers a variety of advantageous characteristics to the host organism. The bacteria have crucial functions in maintaining the integrity of the mucosal barrier, providing essential nutrients such as vitamins, and offering protection against infections. Furthermore, the interplay between commensal microbiota and the mucosal immune system plays a pivotal role in maintaining optimal immunological functionality. The bacteria present in the colon exhibit the expression of carbohydrate-active enzymes, which equip them with the capacity to undergo fermentation of intricate carbohydrates, resulting in the production of metabolites such as SCFAs.[20] The GI tract normally contains three primary SCFAs, propionate, butyrate, and acetate, which are commonly present in a ratio of 1:1:3.[21] These fatty acids are promptly taken up by epithelial cells in the GI tract. Once absorbed, they play a crucial role in regulating several cellular processes, including gene expression, chemotaxis, differentiation, proliferation, and apoptosis.[22] The gastrointestinal microbiota plays a vital role in the production of critical vitamins that the host organism is unable to produce on its own.[23] Lactic acid bacteria play a crucial role in manufacturing vitamin B12, a compound not naturally produced by animals, plants, or fungi.[23] Numerous lines of evidence substantiate the notion that the gut microbiota plays a significant role in modulating epithelial homeostasis.[24] Mice that are devoid of germs demonstrate a compromised process of epithelial cell turnover, which may be restored upon colonization with microbiota.[25] Bacteria have been shown to have a significant role in facilitating cell regeneration and wound healing, as shown by the instance of *Lactobacilli rhamnosus* GG.[26] Moreover, there have been indications that other species, including A. *muciniphila*[27] and *Lactobacillus plantarum*,[28] have a role in enhancing epithelial integrity. Furthermore, it has been suggested that bacteria have the ability to control not just the qualities of epithelial cells but also the properties and turnover of mucus.

Gut hypothesis and inflammation in heart failure

Scientific findings about the presence of a mucus layer between the gut microbiome and epithelium unfolded the old concept of direct adherence of the gut microbiome with mucosal epithelium.[29] Mucus layered epithelium along with gut microbes and certain immune cells in lamina propria are collectively highlighted as the gut barrier demonstrating a shred of fundamental evidence in the maintenance of gut homeostasis.[30]

Mucosal epithelium strengthens the gut barrier due to inter-cellular junctions, co-transporters, and various receptors.[31] Among the factors influencing the gut barrier, microbiota's role is incredible and currently gaining attention from the scientific community in both human health and disease. Microbiomes not only control pathogenicity by preventing the colonization of microbes, neutralizing microbial antigens, and producing antimicrobial products but also inculcate a complementary component of the barrier, the mucin.[32] Several biological and mechanical factors trigger disturbances in this barrier and expose the bloodstream directly to noxious stimuli, which develops progressive cascades of chronic inflammation. Recent data is suggestive of a similar mechanistic linkage with cardiovascular morbidity, especially HF.[33]

Our thinking over the past years is congruent with the fact that the gut microbiome is directly contributing to pathogenesis and the progression of heart failure, a leading cause of morbidity and mortality all over the world.[34] HF-associated hemodynamic imbalance induces hypoxia and congestion of the bowel wall, especially villi, which are more prone to ischemia. This intestinal hypoperfusion state leads to distortion of the intestinal mucosa and ultimately deteriorates the integrity of the gut barrier.[35,36] Moreover, recent data explored the presence of edematous, collagenous, and thick-walled intestinal mucosa in HF entities.[36] Such histopathological erosions

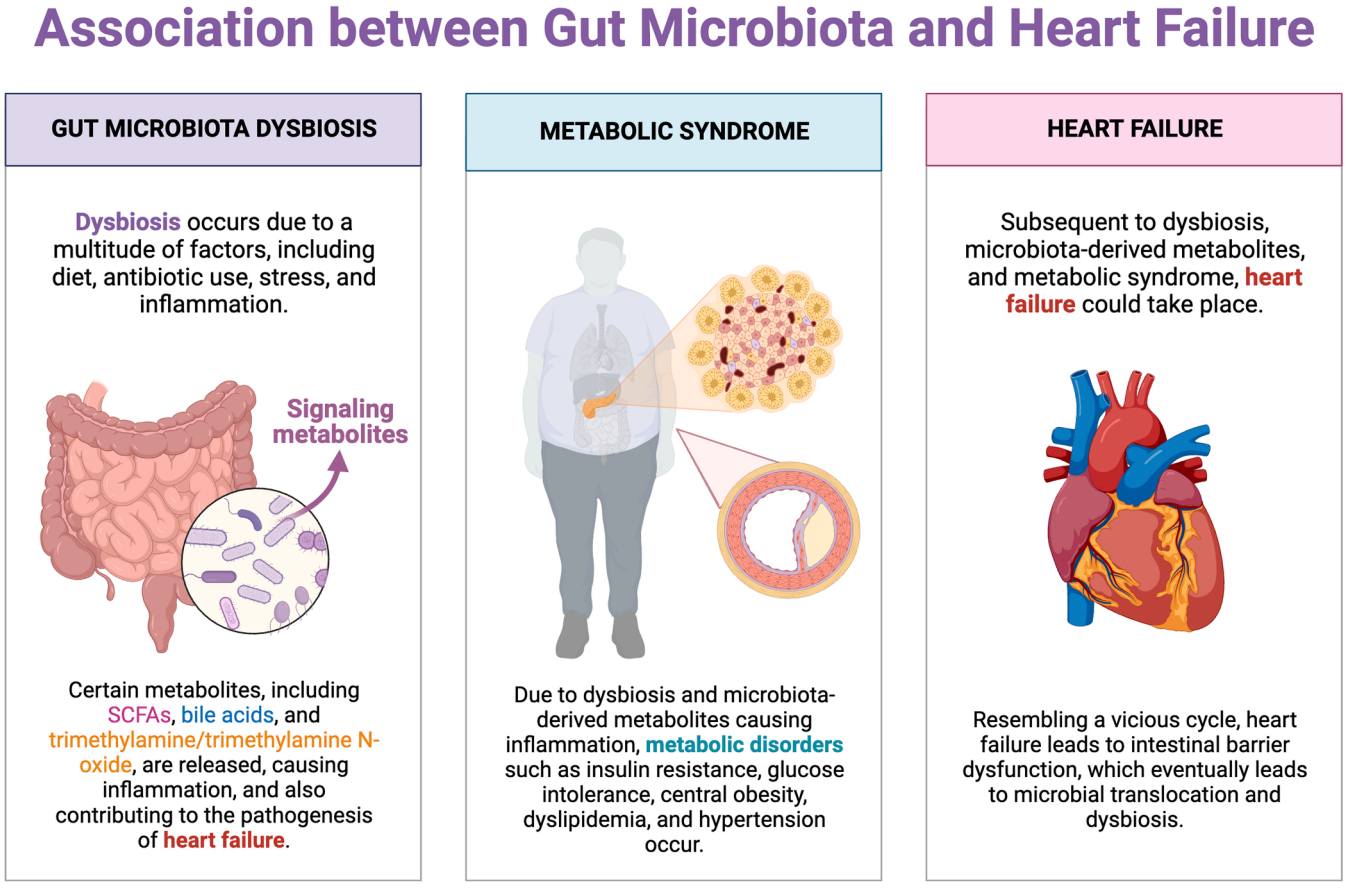

Fig. 1. Association between gut microbiota and heart failure. Gut microbiota dysbiosis can occur due to multiple causes, which lead to a release of certain signalling metabolites that lead to the development of inflammation and metabolic disorders like insulin resistance, central obesity etc. Subsequent to these changes, heart failure could take place which paves the way for the development of a vicious cycle of intestinal barrier dysfunction with dysbiosis and inflammation.

Table 3
Techniques for studying microbiome composition and function.

Technique	Description
Marker Gene Analysis	Involves targeted sequencing of specific genes, such as the 16S rRNA gene for bacteria or the ITS region for fungi. These genes serve as unique barcodes for taxonomic identification.
Shotgun Metagenomics	An untargeted sequencing method that captures all genetic information from a microbiome sample, allowing the study of bacteria, fungi, DNA viruses, and other microbes.
Metatranscriptomics	Captures RNA transcribed from microbial cells, enabling assessment of gene expression activities within the microbiome.
Metabolomics	Focuses on profiling the metabolites produced by the microbiota and their interactions with host metabolism, often using mass spectrometry for identification.
Metaproteomics	Identifies and quantifies the proteins present within a microbiome, also utilizing mass spectrometry for protein analysis.

were rationalized in the disintegration of the barrier which transforms the intestine into a leaky gut and consequently translocation to systemic circulation.[37]

Translocated microbiota endotoxin-associated inflammation and progression of HF heightens a vicious cycle by evolving multiple complex immune-mediated pathways.[38] Immune-mediated cytokines make the gut more permeable and acidosis secondary to ischemic hypoxia worsens decompression of the heart by absorption of sodium and water via sodium-hydrogen exchanger 3 (NHE-3).[39] In addition, reduced ejection fraction was documented by a direct attack of lipopolysaccharides (LPS) on cardiomyocytes.[40] Consequently, a correlation exists between the gastrointestinal system and the cardiovascular system which could be the basis for further diagnostic and therapeutic interventions in patients with HF.

Various patterns were expressed in gut dysbiosis with increased enteropathogenic organisms, specifically Shigella, Salmonella, Yersinia, and Candida species.[41] A reduced spectrum of normal flora including *Coriobacteriaceae, Erysipelotrichaceae, and Ruminococcaceae* at family levels, and *Blautia, Collinsella,* unclassified *Erysipelotrichaceae*, unclassified *Ruminococcaceae* at the genus level was documented by Huang Z et al. in HF patients.[42] A statistical analysis based on 16SrDNA detected a decrease in *Eubacterium rectale* and *Dorea longicatena* SCFA-producing bacteria, in twenty-two hospitalized patients with HF.[43] Sandek et al. also experienced bacterial overgrowth and adhesions in the gut of HF patients.[10] Another data-based study observed the rise of Trimethylamine N -oxide (TMAO) producing microbial and the decline of SCFA-producing bacteria which resultantly aggravates the progression of HF. Different infections, drugs, diet, acid-base imbalance, and gastroparesis were highlighted as igniting elements in gut dysbiosis and the progressive nature of HF.[44]

Recent evolution in modern research showed a significant role of microbiota metabolite in the pathophysiology of HF. TMAO, secondary bile acids, and SCFA have been marked as a modulator in the lives of patients living with HF.[45]

Interesting impacts of gut microbiota-modified TMAO were experienced on cardiac remodelling. Li et al. observed cardiac hypertrophy and fibrosis while Orange et al. expressed Left ventricular dilatation with reduced ejection fraction secondary to TMAO.[46] Raised levels of TMAO in HF with reduced ejection fraction (HFrEF) were found significant in both diagnosis and prognosis observed by Salzano et al.[46] Serum TMAO Levels could be the pharmacological and dietary target in order to hinder the progression of HF.[47,48]

Conflicting outcomes were correlated by different researchers regarding the effect of secondary bile acids on HF patients. Some studies favoured post-cardiac injury-affiliated apoptotic and pro-fibrotic roles, while others valued positive feedback over cardiac remodelling, hypertrophy, and survivability.[44,48] Hence, more clinical trial needs to be focused on recognizing bile acids as a prognostic and therapeutic factor. The latest studies suggested satisfactory results in preventing mineralocorticoid-induced cardiac hypertrophy and fibrosis regarding SCFA.[49] Marques et al. determined improved microbiota in patients with a high-fiber diet.[50] Another study conducted on 84 patients with HF explored that a low-fibre diet caused microbiota dysbiosis.[51]

Apart from its role in cardiac pathology, SCFA also modulates systemic inflammation by activating various mechanisms that involve recruiting leukocytes, expressing adhesion molecules, secreting cytokines (IL-10,1L-2, TNF-alpha) and chemokines (e.g., MCP-1). These fatty acids cause apoptosis of chronic inflammatory cells, especially lymphocytes and macrophages, which might be helpful in controlling systemic inflammation.[52] Orekhov et al. and Rahman et al. documented inflammation, oxidative stress secondary to mitochondrial damage, and various complement pathways as the basis of atherosclerosis and cancer.[53,54] SCFA lessens the cumulative inflammatory responses and plays a key role in plaque formation and tumor aggression as emphasized by O'Sullivan et al. and Eikawa et al.[55,56]

Clinical application of SCFA in different forms might be beneficial in inflammatory bowel disease by providing mucosal protection and declining gut inflammation, but further pharmacokinetics need to be explored.[52] Matson et al. showed the effect of SCFA on melanoma patients.[57] Different studies in rats expressed astonishing results of SCFA in different diseases, specifically septic shock, and acute lung injury (ALI) secondary to sepsis.[58] Marked fall in infarct size and reperfusion injury was described by Hu et al. in rats.[59] SCFA might be beneficial in preventing cerebral fibrosis by de-activating microglial cells in rats with cerebral infarct. Clinical trials must be conducted to design new drug therapies for cardiac and cerebral advancements.

Precision nutrition in heart failure

A subsect of precision medicine, "precision nutrition" aims to individualize diet plans based on phenotype, thereby maximizing therapeutic benefits and bettering prognoses.[60] It employs metabolomic, proteomic, and genomic data; the impact of gut flora on cardiovascular health is one such facet of the study.[60]

Nutritional interventions in patients with HF in the form of prebiotics, probiotics, and synbiotics have been elaborated in the

literature.[9,61,62] Probiotics are live microbes that are administered to manipulate the gut microflora and to confer health benefits.[61] Studies conducted in rats have shown probiotics to reduce cardiac remodelling after ischemic injuries.[62] Similarly, *Saccharomyces boulardii* given to chronic HF patients resulted in improved LVEF and decreased left atrial (LA) diameters.[9] Other studies on animals with moderate HF that had undergone coronary artery ligation without reperfusion proved that there were reductions in HF parameters and ventricular remodelling.[63] A randomized trial by Constanza et al. also demonstrated that HF indices, namely cardiac output, LVEF, LA diameter, stroke volume, etc. tended towards their normal range following administration *of L. rhamnosus GR-1 and L. plantarum 299v*.[64] It has been hypothesized that these advantageous effects are due to probiotics causing a fall in leptin levels.[32]

Nitric oxide (NO) is a potent vasodilator, which can be derived from dietary inorganic nitrates by oral and intestinal bacteria. Its benefits in endothelial function and blood pressure reduction contribute to its cardioprotective effects, therefore rendering microbes such as *Veillonella* and *Actinomyces* which reduce nitrates potential candidates for consideration as probiotics.[63]

Prebiotics are non-digestible products that promote the growth of probiotics, selectively modify microbial composition, and function, or induce the growth of certain microbes.[32] Prebiotics like vitamins, iron, zinc, unsaturated fatty acids, inulin, etc. facilitate immunity and regulate stress responses thus modulating oxidative stress, renin-angiotensin system overactivity, inflammatory reactions, vascular resistance, and other such factors that influence cardiovascular health.[61] Synbiotics are a combination of pro- and prebiotics. Postbiotics refer to metabolites derived from microorganisms that are beneficial to the host. They are the active component of probiotics and, hence, are equally effective, but are devoid of adverse effects since they do not contain live organisms.[61]

The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to provide mortality benefits for HF patients, especially those with hypertensive HFpEF.[65] A decrease in markers for cardiac injury and strain like high sensitivity cardiac troponin1 and N-terminal b-type pro natriuretic peptide has been noted with DASH diets.[60] Low sodium intake results in blood pressure reduction and subsequently improved LV function; additional benefits include improvement in arterial compliance, oxidative stress, and quality of life.[60] The Mediterranean diet, owing to its ability to lower trimethylamine-N-oxide levels has also been employed for primary prevention of HF.[32]

Precision heart failure therapeutics

Several studies have proved the beneficial effect of high-fibre diets on gut flora and its impact on HF; positive effects on cardiac function, remodelling, systolic and diastolic functions, as well as hypertrophic and dilatation changes have been noted.[66] A diet rich in fibers decreases pathogenic species and increases symbiotic bacteria, some of which, like the acetate-producing bacteria, protects against myocardial hypertrophy and fibrotic development.[67] A calorie-dense obesogenic diet (OBD) has the contrary effect on intestinal microbial composition, causing cardiac fibrosis and decreased LVEF.[66] Oral charcoal adsorbents like AST-120 have been shown to reduce hypertrophic and fibrotic changes in animal models by altering the concentration of select microbiota metabolic products.[68]

Fecal Microbiota Transplantation (FMT) is a method to introduce healthy gut flora into a patient to improve their microbiome composition.[68] Trials have been conducted to study the role of FMT in CVD; myocardial injury due to inflammatory infiltration has been notably reduced following the procedure and peripheral resistance to insulin was seen to improve following faecal infusion.[68,69] FMT is thus a promising avenue of therapeutics; however, it is not without risks.[61,68] Pathogenic and unwanted bacteria may be transferred, causing disease and mortality.[61,68] Further research is required for the development of better screening methods for donor faeces, non-invasive delivery methods, and exploration of techniques such as single-species transplants.

Trimethylamine N-oxide

TMAO is synthesized in the gut via a two-step procedure.[61] First, dietary precursors such as choline, L-carnitine, and phosphatidylcholine are converted to TMA by the gut floral enzyme system CutC/D (TMA lyases).[61] The cholines can be directly converted to TMA, but L-carnitine forms an intermediate γ-butyrobetaine, which subsequently forms TMA.[61] Choline is the most common dietary precursor and is found in eggs, dairy, and fish; red meat has high levels of L-carnitine.[34,69] Choline also undergoes enterohepatic circulation, which can result in TMAO synthesis long after oral intake.[34] Next, the hepatic flavin-containing monooxygenases (FMO) oxidize TMA to TMAO which can be excreted by the kidneys or stored in tissues.[61]

TMAO exerts its detrimental effects - cardiac remodelling, mitochondrial dysfunction, fibrosis, and hypertrophy via the transforming growth factor-β1 (TGF-β1)/Smad3 pathway.[34,70] Elevated levels have been linked to poorer acute and chronic HF prognoses and are thus a predictor for severity, complications, and mortality.[34] Murine studies conducted to support these theories have demonstrated that TMAO causes reversible LV dilation, and increased BNP levels.[70] Thus, it has been concluded that dietary modification control can be achieved on circulating TMAO levels which results in improvement in myocardial and LV functions and BNP levels.[70]

Vegan diets eliminate major sources of TMAO precursors and result in a microbiome that has a lower capacity to synthesize it.[69] In-vivo synthesis can be blocked by targeting either the gut floral or the hepatic enzymes. Inhibition of the hepatic enzymes, however, can lead to TMO accumulation in the liver and may result in hepatitis.[68] Iodomethylcholine, Fluoromethylcholine and 3,3-dimethyl-1--butamol (DMB) are non-lethal TMA lyase inhibitors.[34,70] DMB is a competitive CutC inhibitor that does not affect commensal populations and has been shown to suppress TMAO production and prevent cardiac remodelling.[70]

Antibiotics lead to only a transient decrease in TMAO because synthesis re-starts after resistant strains begin proliferating.[70] Other prospective therapeutic modalities include meldonium, a carnitine and γ-butyrobetaine analog, which inhibits the TMAO synthesis pathway, and resveratrol, which alters the microbiome.[32]

Gut microbiome-related heart failure biomarkers

Gut microbiota can also influence the host by generating bioactive metabolites. These metabolites may potentially influence intestinal well-being, immune system function, and even the cardiovascular system.[71]

Short-chain fatty acid

In a recent prospective study conducted by Modrego et al., an increase in SCFA levels in the body, especially butyrate, was associated with a favorable prognosis in patients diagnosed with HF.[72] Their data indicated that the improved prognosis and reduction of inflammation 12 months after an initial episode of HF were linked to the recovery of the gut microbiota composition. This recovery was marked by an increase in the presence of beneficial bacteria and short-chain fatty acids (SCFAs), along with a decrease in the prevalence of pathogenic bacteria. In a separate study conducted by Bartolomaeus et al. using rat models, it was observed that SCFAs, particularly propionate, notably reduced cardiac hypertrophy, fibrosis, vascular dysfunction, and hypertension.[73] These findings imply that promoting increased SCFA production might serve as a beneficial non-pharmacological preventive approach for individuals with heart failure.

Phenylalanine

In recent studies, higher phenylalanine concentrations have been found in patients with advanced heart failure than in healthy individuals.[74,75] The study conducted by Czibik et al. established a pathogenic role of increased phenylalanine levels leading to cardiac aging, thus highlighting phenylalanine modulation as a potential therapeutic strategy for age-associated cardiac impairment.[76] Hiraiwa et al. conducted an observational study to understand the significance of the leucine/phenylalanine ratio as a prognostic tool for diagnosing HF. Their findings revealed that a leucine/phenylalanine ratio of less than 1.7 was linked to an increased risk of death and hospitalization due to worsening HF, whereas a ratio exceeding 1.7 was associated with a lower risk of experiencing the same outcomes. Consequently, these results suggest that this ratio could serve as a valuable predictor of future cardiac events in patients with HF.[77]

Ricinoleic acid

Ricinoleic acid (RA), a gut microbiota metabolite and the main component of castor oil is known to exert remarkable analgesic and anti-inflammatory effects.[78] Levels of ricinoleic acid have been reported to be significantly decreased in patients with chronic HF.[79] Moreover, ricinoleic acid levels were negatively associated with bacterial communities found to be enriched in the gut of patients with chronic HF and positively correlated with those present in the microbiota of healthy patients without any underlying cardiovascular pathology.[80]

Other gut microbiota metabolites associated with heart failure

Wang et al. concluded that bacteria found in higher quantities in the gut of HF patients, such as Escherichia, Shigella, and Klebsiella, were negatively correlated with serum biocytin and riboflavin levels. Haemophilus also exhibited a negative correlation with serum levels of alpha-lactose, cellobiose, isomaltose, lactose, melibiose, sucrose, trehalose, and turanose, potentially suggesting a cardioprotective effect of these metabolites.[81] In contrast, Klebsiella demonstrated a positive correlation with serum bilirubin and ethyl salicylate levels, which may indicate a detrimental impact of these metabolites on cardiovascular outcomes in patients. These metabolites warrant further research for the development of therapeutics aimed at blocking their action, potentially offering cardioprotective benefits.[80]

Pharmacology and its effects on gut microbiome

The gut microbiome affects the pharmacokinetics and pharmacodynamics of over 50 drugs, despite being overlooked.[82] Solubility, pH, transit time, permeability, and microbial metabolism all have an impact on drug absorption. The gut microbiota can alter drug efficacy and safety.[83] It can, for example, limit drug absorption, as demonstrated by digoxin and *eggerthella lenta*.[84] Microbes also have an impact on drug metabolism and distribution, such as in the case of benzodiazepines used to treat inflammatory bowel disease.[85] Furthermore, microbial metabolites can disrupt host drug metabolism.[85] The microbiota can influence drug metabolism indirectly by affecting liver enzyme expression.[86] Understanding these interactions is critical for personalized medicine and drug therapy optimization.

It is unclear how the microbiome affects pharmaceutical responses, especially in cardiovascular medicine. Dutch research on 1,135 patients found that beta-blockers, ACE inhibitors, statins, and platelet inhibitors dramatically affect the gut microbiome.[87] An investigation with 2,700 British TwinsUK participants confirmed this.[88]

Statins

The gut microbiota may alter three of the most prescribed statins—atorvastatin, rosuvastatin, and simvastatin—according to

studies. When taken with simvastatin, the bile acids lithocholic, taurolithocholic, and glycolithocholic, which are all made by bacteria, lower LDL-C. On the other hand, genetic variations like the SNP gene that codes for the transporter SLCO1B have an impact on statin response and bile acid levels as well.[89] A study by Nolan et al. showed how statin in a mouse model affected the composition of the gut microbe and reduced hepatic expression of CYP27a1.[90] Similarly, a study by Liu et al. showed that rosuvastatin changed bacterial taxonomy, influencing LDL-C levels.[91] In animal studies, atorvastatin influenced gut microbial populations.[92] These data demonstrate a link between gut microbiota, statins, and treatment outcomes.

Amlodipine and captopril

The gut microbiota and certain antihypertensive medicines are poorly understood, largely based on animal research. Amlodipine is well absorbed in the digestive tract, but it decreases with time in rat and human faeces. Amlodipine absorption increased in rats administered ampicillin, a medication that suppresses the gut microbiota, prior to amlodipine, indicating that the gut microbiota influences drug absorption.[93] Similarly, a study by Santisteban et al. showed that captopril therapy increased the length of the villi and decreased intestinal permeability and fibrosis in rats with high blood pressure. This fixed the dysbiotic state that comes with high blood pressure.[94]

Warfarin, aspirin, and indomethacin

Warfarin, a thromboembolic disease anticoagulant, can interact with antibiotics, increasing the risk of bleeding events. Antibiotics may interfere with warfarin metabolism via CYP enzymes or disrupt vitamin K-producing gut microorganisms.[95] Aspirin, an anti-platelet medication used to treat cardiovascular disease, may cause injury to the upper GI tract due to its effect on gut flora.[96] Aspirin and other NSAIDs influence the gut microbiome. Prevotella, Bacteroides, Ruminococaceae, and Barnesiella are four bacteria that can distinguish aspirin users from non-users.[97] Indomethacin, another nonsteroidal anti-inflammatory medicine, was discovered to have bidirectional effects on the intestinal microbiota; it altered the microbiome, which influenced indomethacin metabolism. In the gastrointestinal tract, glucuronidases deconjugate indomethacin metabolites, enhancing drug exposure.[98] Although hereditary factors have a role in aspirin resistance, the gastrointestinal microbiome's contribution to aspirin responsiveness is not entirely known.[99]

Digoxin

Digoxin is a well-known medication for treating heart failure whose absorption depends on gut bacteria. *Eggerthella lenta* changes digoxin into the inactive microbial metabolite dihydrodigoxin, which stops 10% of patients' bodies from absorbing the drug.[84] Digoxin turns on the cardiac glycoside reductase (cgr), which is a cytochrome-encoding operon that is missing *in E. lenta* strains that do not reduce but are present in strains that do reduce. This is what makes digoxin work. Digoxin taken with antibiotics or an arginine-rich diet stops this microbial response, which raises systemic digoxin levels and causes changes in drug levels that are clinically important.[89]

Ongoing trials and their implications in HF management

Continuous evolution in the HF research landscape supports evidence that the gut microbiome plays a vital role in the progression of HF. Recently, several noteworthy studies have explored the association between heart failure and gut microbiome. In patients with HFpEF, the GutHeart trial[100] aimed to investigate whether modulating the gut microbiota improves cardiac function. This study, involving a three-month intervention with either the probiotic yeast S. boulardii or the locally acting oral antibiotic rifaximin, showed no significant benefits of gut microbiota modification for HF management. However, it revealed a complex relationship between gut and heart health. Similarly, a pioneering study,[101] is investigating the role of altered gut microbiota in the initiation and establishment of HF and pre-HFpEF. If this hypothesis is validated, monitoring gut microbiota could serve as an early detection tool for individuals at risk of developing HF or pre-HFpEF. Additionally, this could lead to the development of preventive strategies, such as dietary interventions or probiotics, to modulate the microbiome and reduce the risk of HF. Another trial, PROBHF,[102] explored the potential of probiotics as adjunctive therapy for patients with advanced HF. If their hypothesis that daily probiotic supplementation will lead to favourable changes in various biomarkers related to inflammation and cardiac function in HF patients compared to a placebo group is supported, it could lead to new strategies for managing heart failure, with a focus on inflammation, nutrition, and patient well-being.

EMPAGUM[103] suggested that empagliflozin, a drug primarily used for diabetes, might affect the gut microbiota in patients with HFpEF. If a link between empagliflozin-induced changes in gut microbiota and improved HFpEF outcomes is established, it could open new avenues for tailored HF management strategies. While it is also essential to acknowledge the critical role of preoperative optimization in enhancing the overall quality of care and outcomes for patients with HF, a study in China[104] supports those proactive preoperative interventions, particularly focusing on nutrition and immune enhancement, can potentially improve the outcomes of HF patients undergoing LVAD surgery.

To shed light on new potential treatments for patients with ischemic heart failure, a trial[105] investigated the differential metabolic markers associated with ischemic HF and the influence of faecal flora on the course of heart failure in patients with ischemic HF. While promising, these findings suggest the need for further research to establish causal relationships and to better understand the mechanisms involved. Clinical trials and studies with larger patient populations are essential to validate these hypotheses.

Conclusion and future directions

In conclusion, our study demonstrates the importance of considering the extent and ways dysbiosis could contribute to the pathophysiology of HF through inducing systemic inflammation, oxidative stress, and the accumulation of specific metabolites, which all concludingly may exacerbate the severity of cardiac dysfunction in patients and worsen their prognosis. Therefore, observing the complex interplay between gut microbiota and the pathogenesis of HF could provide valuable knowledge regarding 1) prospective prevention and treatment schemes, 2) novel use of gut microbiota as biomarkers, and 3) our understanding of HF. Potential therapeutic avenues include dietary interventions, such as including supplements including probiotics and prebiotics, in addition to faecal microbiota transplantation, antibiotics, and lifestyle modifications, which could all contribute to the modulation of gut microbiota. Furthermore, integrating such interventions into clinical practice could assist physicians in revolutionizing the quality of care provided to patients, and thereby improving outcomes for patients suffering from such challenging conditions. It is also imperative to acknowledge that understanding how medications impact the gut microbiota and the subsequent effects of such impact could update the strategies for providing optimal management regimens. Further study is needed to understand how gut bacteria affect the body, how they might be controlled, and how they improve patient outcomes. More randomized controlled studies might shed light on gut microbiota's function in HF's genesis and progression and its interactions with cardiovascular disease drugs. Additional studies might examine the role gut microbiota plays in the etiology of various comorbidities that aggravate HF, preserving an understanding of the many processes involved in HF.

Declaration of generative AI in scientific writing

None.

CRediT authorship contribution statement

Hritvik Jain: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Mohammed Dheyaa Marsool Marsool:** Methodology, Writing – original draft, Writing – review & editing, Supervision. **Aman Goyal:** Writing – original draft, Writing – review & editing. **Samia Aziz Sulaiman:** Writing – original draft, Writing – review & editing. **Laveeza Fatima:** Writing – original draft, Writing – review & editing. **Muhammad Idrees:** Writing – original draft, Writing – review & editing. **Bhavya Sharma:** Writing – original draft, Writing – review & editing. **Vamsikalyan Borra:** Writing – original draft, Writing – review & editing. **Prakash Gupta:** Writing – original draft, Writing – review & editing. **Abdullah Nadeem:** Writing – original draft, Writing – review & editing. **Jyoti Jain:** Writing – original draft, Writing – review & editing. **Hassam Ali:** Writing – review & editing, Supervision. **Amir H Sohail:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Eckburg PB, Bik EM, Bernstein CN, et al. Microbiology: diversity of the human intestinal microbial flora. *Science*. 2005;308:1635–1638. https://doi.org/10.1126/science.1110591 (80-).
2. Canfora EE, Meex RCR, Venema K, et al. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat Rev Endocrinol*. 2019;15(5):261–273. https://doi.org/10.1038/s41574-019-0156-z.
3. Hrncir T. Gut microbiota dysbiosis: triggers, consequences, diagnostic and therapeutic options. *Microorganisms*. 2022;10(3):578. https://doi.org/10.3390/microorganisms10030578.
4. DeGruttola AK, Low D, Mizoguchi A, et al. Current understanding of dysbiosis in disease in human and animal models. *Inflamm Bowel Dis*. 2016;22(5):1137–1150. https://doi.org/10.1097/MIB.0000000000000750.
5. Diseases GBo. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392:1789–1858.
6. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93(9):1137–1146. https://doi.org/10.1136/hrt.2003.025270.
7. Shirazi LF, Bissett J, Romeo F, et al. Role of inflammation in heart failure. *Curr Atheroscler Rep*. 2017;19:27. https://doi.org/10.1007/s11883-017-0660-3.
8. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. 2017;474(11):1823–1836. https://doi.org/10.1042/BCJ20160510.
9. Kamo T, Akazawa H, Suda W, et al. Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure. *PLoS One*. 2017;12,e0174099. https://doi.org/10.1371/journal.pone.0174099.
10. Sandek A, Bauditz J, Swidsinski A, et al. Altered intestinal function in patients with chronic heart failure. *J Am Coll Cardiol*. 2007;50:1561–1569. https://doi.org/10.1016/j.jacc.2007.07.016.
11. Sun W, Du D, Fu T, et al. Alterations of the gut microbiota in patients with severe chronic heart failure. *Front Microbiol*. 2022;12, 813289. https://doi.org/10.3389/fmicb.2021.813289.
12. Jandhyala SM, Talukdar R, Subramanyam C, et al. Role of the normal gut microbiota. *World J Gastroenterol*. 2015;21(29):8787–8803. https://doi.org/10.3748/wjg.v21.i29.8787.

13. Arboleya S, Binetti A, Salazar N, et al. Establishment and development of intestinal microbiota in preterm neonates. *FEMS Microbiol Ecol*. 2012;79(3):763–772. https://doi.org/10.1111/j.1574-6941.2011.01261.x.
14. Walker AW, Ince J, Duncan SH, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J*. 2011;5(2):220–230. https://doi.org/10.1038/ismej.2010.118.
15. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–563. https://doi.org/10.1038/nature12820.
16. Klingensmith NJ, Coopersmith CM. The gut as the motor of multiple organ dysfunction in critical illness. *Crit Care Clin*. 2016;32(2):203–212. https://doi.org/10.1016/j.ccc.2015.11.004.
17. Lee YT, Huang SQ, Lin CH, et al. Quantification of gut microbiota dysbiosis-related organic acids in human urine using LC-MS/MS. *Molecules*. 2022;27(17):5363. https://doi.org/10.3390/molecules27175363. Published 2022 Aug 23.
18. Tang Q, Jin G, Wang G, et al. Current sampling methods for gut microbiota: a call for more precise devices. *Front Cell Infect Microbiol*. 2020;10:151. https://doi.org/10.3389/fcimb.2020.00151. Published 2020 Apr 9.
19. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care*. 2010;33(10):2277–2284. https://doi.org/10.2337/dc10-0556.
20. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Micro*. 2014;12(10):661–672. https://doi.org/10.1038/nrmicro3344.
21. Corrêa-Oliveira R, Fachi JL, Vieira A, et al. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunol*. 2016;5(4):e73. https://doi.org/10.1038/cti.2016.17. Published 2016 Apr 22.
22. LeBlanc JG, Milani C, de Giori GS, et al. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. *Curr Opin Biotechnol*. 2013;24(2):160–168. https://doi.org/10.1016/j.copbio.2012.08.005.
23. Natividad JM, Verdu EF. Modulation of intestinal barrier by intestinal microbiota: pathological and therapeutic implications. *Pharmacol Res*. 2013;69(1):42–51. https://doi.org/10.1016/j.phrs.2012.10.007.
24. Smith K, McCoy KD, Macpherson AJ. Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. *Semin Immunol*. 2007;19(2):59–69. https://doi.org/10.1016/j.smim.2006.10.002.
25. Swanson 2nd PA, Kumar A, Samarin S, et al. Enteric commensal bacteria potentiate epithelial restitution via reactive oxygen species-mediated inactivation of focal adhesion kinase phosphatases. *Proc Natl Acad Sci USA*. 2011;108(21):8803–8808. https://doi.org/10.1073/pnas.1010042108.
26. Reunanen J, Kainulainen V, Huuskonen L, et al. Akkermansia muciniphila adheres to enterocytes and strengthens the integrity of the epithelial cell layer. *Appl Environ Microb*. 2015;81(11):3655–3662. https://doi.org/10.1128/AEM.04050-14.
27. Chen HQ, Yang J, Zhang M, et al. Lactobacillus plantarum ameliorates colonic epithelial barrier dysfunction by modulating the apical junctional complex and PepT1 in IL-10 knockout mice. *Am J Physiol Gastrointest Liver Physiol*. 2010;299(6):G1287–G1297. https://doi.org/10.1152/ajpgi.00196.2010.
28. Zhao P, Zhao S, Tian J, et al. Significance of gut microbiota and short-chain fatty acids in heart failure. *Nutrients*. 2022;14(18):3758. https://doi.org/10.3390/nu14183758. Sep 11PMID: 36145134; PMCID: PMC9504097.
29. Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut*. 2020;69(12):2232–2243. https://doi.org/10.1136/gutjnl-2020-322260. DecEpub 2020 Sep 11. PMID: 32917747; PMCIDPMC7677487.
30. Di Tommaso N, Gasbarrini A, Ponziani FR. Intestinal barrier in human health and disease. *Int J Environ Res Public Health*. 2021;18(23):12836. https://doi.org/10.3390/ijerph182312836. Dec 6PMID: 34886561; PMCIDPMC8657205.
31. Martel J, Chang SH, Ko YF, et al. Gut barrier disruption and chronic disease. *Trends Endocrinol Metab*. 2022;33(4):247–265. https://doi.org/10.1016/j.tem.2022.01.002. AprEpub 2022 Feb 9. PMID: 35151560.
32. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol*. 2019;16(3):137–154. https://doi.org/10.1038/s41569-018-0108-7. MarPMID: 30410105; PMCID: PMC6377322.
33. Nagatomo Y, Tang WH. Intersections between microbiome and heart failure: revisiting the gut hypothesis. *J Card Fail*. 2015;21(12):973–980. https://doi.org/10.1016/j.cardfail.2015.09.017. DecEpub 2015 Oct 3. PMID: 26435097; PMCID: PMC4666782.
34. Chaikijurajai T, Tang WHW. Gut microbiome and precision nutrition in heart failure: hype or hope? *Curr Heart Fail Rep*. 2021;18(2):23–32. https://doi.org/10.1007/s11897-021-00503-4. AprEpub 2021 Feb 9. PMID: 33559845.
35. Xu H, Wang X, Feng W, et al. The gut microbiota and its interactions with cardiovascular disease. *Microb Biotechnol*. 2020;13(3):637–656. https://doi.org/10.1111/1751-7915.13524. MayEpub 2020 Jan 26. PMID: 31984651; PMCID: PMC7111081.
36. Rahman MM, Islam F, -Or-Rashid MH, et al. The gut microbiota (microbiome) in cardiovascular disease and its therapeutic regulation. *Front Cell Infect Microbiol*. 2022;12, 903570. https://doi.org/10.3389/fcimb.2022.903570. Jun 20PMID: 35795187; PMCID: PMC9251340.
37. Tang WH, Kitai T, Hazen SL. Gut microbiota in cardiovascular health and disease. *Circ Res*. 2017;120(7):1183–1196. https://doi.org/10.1161/CIRCRESAHA.117.309715. Mar 31PMID: 28360349; PMCID: PMC5390330.
38. Matsiras D, Bezati S, Ventoulis I, et al. Gut failure: a review of the pathophysiology and therapeutic potentials in the gut-heart axis. *J Clin Med*. 2023;12(7):2567. https://doi.org/10.3390/jcm12072567. Mar 29PMID: 37048650; PMCID: PMC10095379.
39. Polsinelli VB, Marteau L, Shah SJ. The role of splanchnic congestion and the intestinal microenvironment in the pathogenesis of advanced heart failure. *Curr Opin Support Palliat Care*. 2019;13(1):24–30. https://doi.org/10.1097/SPC.0000000000000414. MarPMID: 30640740; PMCID: PMC6366455.
40. Avlas O, Fallach R, Shainberg A, et al. Toll-like receptor 4 stimulation initiates an inflammatory response that decreases cardiomyocyte contractility. *Antioxid Redox Signal*. 2011;15(7):1895–1909. https://doi.org/10.1089/ars.2010.3728. Oct 1Epub 2011 Apr 21. PMID: 21126202.
41. Pasini E, Aquilani R, Testa C, et al. Pathogenic gut flora in patients with chronic heart failure. *JACC Heart Fail*. 2016;4(3):220–227. https://doi.org/10.1016/j.jchf.2015.10.009. Epub 2015 Dec 9. PMID: 26682791.
42. Huang Z, Mei X, Jiang Y, et al. Gut microbiota in heart failure patients with preserved ejection fraction (GUMPTION study). *Front Cardiovasc Med*. 2022;8, 803744. https://doi.org/10.3389/fcvm.2021.803744. Jan 6PMID: 35071367; PMCID: PMC8770938.
43. Francisqueti-Ferron FV, Nakandakare-Maia ET, Siqueira JS, et al. The role of gut dysbiosis-associated inflammation in heart failure. *Rev Assoc Med Bras*. 2022;68(8):1120–1124. https://doi.org/10.1590/1806-9282.20220197 (1992)Sandek A, Anker SD, von Haehling S. The gut and intestinal bacteria in chronic heart failure. Curr Drug Metab. 2009 Jan;10(1):22-8. doi: 10.2174/138920009787048374. PMID: 19149510.
44. Masenga SK, Povia JP, Lwiindi PC, et al. Recent advances in microbiota-associated metabolites in heart failure. *Biomedicines*. 2023;11(8):2313. https://doi.org/10.3390/biomedicines11082313. Aug 21PMID: 37626809; PMCID: PMC10452327.
45. Li Z, Wu Z, Yan J, et al. Gut microbe-derived metabolite trimethylamine N-oxide induces cardiac hypertrophy and fibrosis. *Lab Invest*. 2019;99(3):346–357. https://doi.org/10.1038/s41374-018-0091-y. MarEpub 2018 Aug 1. PMID: 30068915.
46. Salzano A, Cassambai S, Yazaki Y, et al. The gut axis involvement in heart failure: focus on trimethylamine N-oxide. *Cardiol Clin*. 2022;40(2):161–169. https://doi.org/10.1016/j.ccl.2021.12.004. MayPMID: 35465890.
47. Zhang Y, Wang Y, Ke B, et al. TMAO: how gut microbiota contributes to heart failure. *Transl Res*. 2021;228:109–125. https://doi.org/10.1016/j.trsl.2020.08.007. FebEpub 2020 Aug 22. PMID: 32841736.
48. Callender C, Attaye I, Nieuwdorp M. The interaction between the gut microbiome and bile acids in cardiometabolic diseases. *Metabolites*. 2022;12(1):65. https://doi.org/10.3390/metabo12010065. Jan 11PMID: 35050187; PMCID: PMC8778259.
49. Hu T, Wu Q, Yao Q, et al. Short-chain fatty acid metabolism and multiple effects on cardiovascular diseases. *Ageing Res Rev*. 2022;81, 101706. https://doi.org/10.1016/j.arr.2022.101706. NovEpub 2022 Aug 4. PMID: 35932976.
50. Marques FZ, Nelson E, Chu PY, et al. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. *Circulation*. 2017;135(10):964–977. https://doi.org/10.1161/CIRCULATIONAHA.116.024545. Mar 7Epub 2016 Dec 7. PMID: 27927713.

51. Mayerhofer CCK, et al. Low fibre intake is associated with gut microbiota alterations in chronic heart failure. *ESC Heart Fail*. 2020;7(2):456–466. https://doi.org/10.1002/ehf2.12596.
52. Vinolo MA, Rodrigues HG, Nachbar RT, et al. Regulation of inflammation by short chain fatty acids. *Nutrients*. 2011;3(10):858–876. https://doi.org/10.3390/nu3100858. OctEpub 2011 Oct 14. PMID: 22254083; PMCID: PMC3257741.
53. Orekhov AN, Poznyak AV, Sobenin IA, et al. Mitochondrion as a selective target for the treatment of atherosclerosis: role of mitochondrial DNA mutations and defective mitophagy in the pathogenesis of atherosclerosis and chronic inflammation. *Curr Neuropharmacol*. 2020;18(11):1064–1075. https://doi.org/10.2174/1570159x17666191118125018. PMID: 31744449; PMCID: PMC7709151.
54. Rahman MM, Islam MR, Shohag S, et al. Microbiome in cancer: role in carcinogenesis and impact in therapeutic strategies. *Biomed Pharmacother*. 2022;149, 112898. https://doi.org/10.1016/j.biopha.2022.112898. MayEpub 2022 Apr 2. PMID: 35381448.
55. O'Sullivan D, Sanin DE, Pearce EJ, et al. Metabolic interventions in the immune response to cancer. *Nat Rev Immunol*. 2019;19(5):324–335. https://doi.org/10.1038/s41577-019-0140-9. MayPMID: 30820043.
56. Eikawa S, Nishida M, Mizukami S, et al. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. *Proc Natl Acad Sci USA*. 2015;112(6):1809–1814. https://doi.org/10.1073/pnas.1417636112. Feb 10Epub 2015 Jan 26. PMID: 25624476; PMCID: PMC4330733.
57. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104–108. https://doi.org/10.1126/science.aao3290. Jan 5PMID: 29302014; PMCID: PMC6707353.
58. Ni YF, Wang J, Yan XL, et al. Histone deacetylase inhibitor, butyrate, attenuates lipopolysaccharide-induced acute lung injury in mice. *Respir Res*. 2010;11(1):33. https://doi.org/10.1186/1465-9921-11-33. PMID: 20302656; PMCID: PMC2848144.
59. Hu X, Xu C, Zhou X, et al. WITHDRAWN: sodium butyrate protects against myocardial ischemia and reperfusion injury by inhibiting high mobility group box 1 protein in rats. *Biomed Pharmacother*. 2010. https://doi.org/10.1016/j.biopha.2010.09.005. Sep 25:S0753-3322(10)00141-1Epub ahead of print. PMID: 20950992.
60. Wickman BE, Enkhmaa B, Ridberg R, et al. Dietary management of heart failure: DASH diet and precision nutrition perspectives. *Nutrients*. 2021;13(12):4424. https://doi.org/10.3390/nu13124424. Dec 10PMID: 34959976; PMCID: PMC8708696.
61. Hsu CN, Hou CY, Hsu WH, et al. Cardiovascular diseases of developmental origins: preventive aspects of gut microbiota-targeted therapy. *Nutrients*. 2021;13(7):2290. https://doi.org/10.3390/nu13072290. Jul 1PMID: 34371800; PMCID: PMC8308390.
62. Gan XT, Ettinger G, Huang CX, et al. Probiotic administration attenuates myocardial hypertrophy and heart failure after myocardial infarction in the rat. *Circ Heart Fail*. 2014;7(3):491–499. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000978. MayEpub 2014 Mar 13. PMID: 24625365.
63. Ettinger G, MacDonald K, Reid G, et al. The influence of the human microbiome and probiotics on cardiovascular health. *Gut Microbes*. 2014;5(6):719–728. https://doi.org/10.4161/19490976.2014.983775. PMID: 25529048; PMCID: PMC4615746.
64. Costanza AC, Moscavitch SD, Faria Neto HC, et al. Probiotic therapy with Saccharomyces boulardii for heart failure patients: a randomized, double-blind, placebo-controlled pilot trial. *Int J Cardiol*. 2015;179:348–350. https://doi.org/10.1016/j.ijcard.2014.11.034. Jan 20Epub 2014 Nov 11. PMID: 25464484.
65. Hummel SL, Seymour EM, Brook RD, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail*. 2013;6(6):1165–1171. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000481. NovEpub 2013 Aug 28. PMID: 23985432; PMCID: PMC4017662.
66. Palombaro M, Raoul P, Cintoni M, et al. Impact of diet on gut microbiota composition and microbiota-associated functions in heart failure: a systematic review of in vivo animal studies. *Metabolites*. 2022;12(12):1271. https://doi.org/10.3390/metabo12121271. Dec 15PMID: 36557307; PMCID: PMC9787978.
67. Drapkina OM, Yafarova AA, Kaburova AN, et al. Targeting gut microbiota as a novel strategy for prevention and treatment of hypertension, atrial fibrillation and heart failure: current knowledge and future perspectives. *Biomedicines*. 2022;10(8):2019. https://doi.org/10.3390/biomedicines10082019. Aug 19PMID: 36009566; PMCID: PMC9406184.
68. Guan X, Sun Z. The role of intestinal flora and its metabolites in heart failure. *Infect Drug Resist*. 2023;16:51–64. https://doi.org/10.2147/IDR.S390582. Jan 5PMID: 36636378; PMCID: PMC9830706.
69. Leshem A, Horesh N, Elinav E. Fecal microbial transplantation and its potential application in cardiometabolic syndrome. *Front Immunol*. 2019;10:1341. https://doi.org/10.3389/fimmu.2019.01341. Jun 14PMID: 31258528; PMCID: PMC6587678.
70. Organ CL, Li Z, Sharp 3rd TE, 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*. 2020;9(10), e016223. https://doi.org/10.1161/JAHA.119.016223. May 18Epub 2020 May 10. PMID: 32390485; PMCID: PMC7660847.
71. 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(4):407–414. Dec 1.
72. Modrego J, Ortega-Hernández A, Goirigolzarri J, et al. Gut microbiota and derived short-chain fatty acids are linked to evolution of heart failure patients. *Int J Mol Sci*. 2023;24(18):13892. Jan.
73. Bartolomaeus H, Balogh A, Yakoub M, et al. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. *Circulation*. 2019;139(11):1407–1421. Mar 12.
74. Wang CH, Cheng ML, Liu MH. Simplified plasma essential amino acid-based profiling provides metabolic information and prognostic value additive to traditional risk factors in heart failure. *Amino Acids*. 2018;50(12):1739–1748. https://doi.org/10.1007/s00726-018-2649-9. DecEpub 2018 Sep 10. PMID: 30203393.
75. Cheng ML, Wang CH, Shiao MS, et al. Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: diagnostic and prognostic value of metabolomics. *J Am Coll Cardiol*. 2015;65(15):1509–1520. https://doi.org/10.1016/j.jacc.2015.02.018. Apr 21PMID: 25881932.
76. Czibik G, Mezdari Z, Murat Altintas D, et al. Dysregulated phenylalanine catabolism plays a key role in the trajectory of cardiac aging. *Circulation*. 2021;144(7):559–574.
77. Hiraiwa H, Okumura T, Kondo T, et al. Prognostic value of leucine/phenylalanine ratio as an amino acid profile of heart failure. *Heart Vessels*. 2021;36(7):965–977.
78. Vieira C, Evangelista S, Cirillo R, et al. Effect of ricinoleic acid in acute and subchronic experimental models of inflammation. *Mediat Inflamm*. 2000;9(5):223–228. https://doi.org/10.1080/09629350020025737. PMID: 11200362; PMCID: PMC1781768.
79. Wu J, Qiu M, Sun L, et al. α-Linolenic acid and risk of heart failure: a meta-analysis. *Front Cardiovas Med*; 2022 [cited 2023 Sep 23];8. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2021.788452.
80. Cui X, Ye L, Li J, et al. Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. *Sci Rep*. 2018;8(1):635. Jan 12.
81. Wang Z, Cai Z, Ferrari MW, et al. The correlation between gut microbiota and serum metabolomic in elderly patients with chronic heart failure. *Mediat Inflamm*. 2021;2021, e5587428. Oct 27.
82. Haiser HJ, Turnbaugh PJ. Developing a metagenomic view of xenobiotic metabolism. *Pharmacol Res*. 2013;69:21–31.
83. Kim D-H. Gut microbiota-mediated drug-antibiotic interactions. *Drug Metab Dispos*. 2015;43:1581–1589.
84. Saha JR, Butler Jr VP, Neu HC, et al. Digoxin-inactivating bacteria: identification in human gut flora. *Science*. 1983.
85. Oz HS, Ebersole JL. Application of prodrugs to inflammatory diseases of the gut. *Molecules*. 2008;13:452–474.
86. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med*. 2005;352:2211–2221.
87. Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*. 2016;352:565–569.
88. Jackson MA, Verdi S, Maxan ME, et al. Gut microbiota associations with common diseases and prescription medications in a population-based cohort. *Nat Commun*. 2018;9:2655.
89. Haiser HJ, Gootenberg DB, Chatman K, et al. Predicting and manipulating cardiac drug inactivation by the human gut bacterium eggerthella lenta. *Science*. 2013;341:295–298.

90. Nolan JA, Skuse P, Govindarajan K, et al. The influence of rosuvastatin on the gastrointestinal microbiota and host gene expression profiles. *Am J Physiol Gastrointest Liver Physiol*. 2017;312:G488–G497.
91. Liu Y, Song X, Zhou H, et al. Gut microbiome associates with lipid-lowering effect of rosuvastatin in vivo. *Front Microbiol*. 2018;9:530.
92. Fu ZD, Cui JY, Klaassen CD. Atorvastatin induces bile acid-synthetic enzyme cyp7a1 by suppressing fxr signaling in both liver and intestine in mice. *J Lipid Res*. 2014;55:2576–2586.
93. Yoo HH, Kim IS, Yoo DH, et al. Effects of orally administered antibiotics on the bioavailability of amlodipine: Gut microbiota-mediated drug interaction. *J Hypertens*. 2016;34:156–162.
94. Santisteban MM, Qi Y, Zubcevic J, et al. Hypertension-linked pathophysiological alterations in the gut. *Circ Res*. 2017;120:312–323.
95. Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *Am J Med*. 2014;127:657–663.e652.
96. Watanabe T, Tanigawa T, Nadatani Y, et al. Risk factors for severe nonsteroidal anti-inflammatory drug-induced small intestinal damage. *Dig Liver Dis*. 2013;45:390–395.
97. Rogers MAM, Aronoff DM. The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clin Microbiol Infect*. 2016;22:e171–e178, 178e179.
98. Liang X, Bittinger K, Li X, et al. Bidirectional interactions between indomethacin and the murine intestinal microbiota. *eLife*. 2015;4:e08973.
99. Beitelshees AL, Voora D, Lewis JP. Personalized antiplatelet and anticoagulation therapy: applications and significance of pharmacogenomics. *Pharmgenomics Pers Med*. 2015;8:43–61.
100. Awoyemi A, Mayerhofer C, Felix AS, et al. *Rifaximin or Saccharomyces Boulardii in Heart Failure with Reduced Ejection Fraction: Results from the Randomized Gutheart Trial*. U.S. National Library of Medicine; 2021 [cited 2023 Sept 22]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8339250/.
101. The role of Gut Microbiota in heart failure and pre-heart failure with preserved ejection fraction - full text view [Internet]. 2023 [cited 2023 Sept 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02728154.
102. Probiotics and inflammatory status in patients with heart failure - full text view [Internet]. 2023 [cited 2023 Sept 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03968549.
103. Empagum: Effects of empagliflozin on gut microbiota in heart failure with a preserved ejection fraction - full text view [Internet]. 2023 [cited 2023 Sept 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05584319.
104. Enhanced nutritional optimization in LVAD trial - full text view [Internet]. 2023 [cited 2023 Sept 22]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05655910.
105. Correlation of Intestinal Flora and Metabolomics in Patients With Ischemic Heart Failure [Internet]. 2023 [cited 2023 Sept 22]. Available from: https://www.clinicaltrials.gov/study/NCT04962763.