The Implication of Gut Microbiome in Heart Failure

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Heart failure (HF) is a worldwide health problem with important consequences for the overall wellbeing of affected individuals as well as for the healthcare system. Numerous pieces of evidence have demonstrated that the associated gut microbiota represent an important component of human physiology and metabolic homeostasis, and can affect one's state of health or disease directly, or through their derived metabolites. The advances in human microbiome studies shed light on the relationship between the gut microbiota and the cardiovascular system, revealing its contribution to the development of heart failure-associated dysbiosis. HF has been linked to gut dysbiosis, low bacterial diversity, intestinal overgrowth of potentially pathogenic bacteria and a decrease in short chain fatty acids-producing bacteria. An increased intestinal permeability allowing microbial translocation and the passage of bacterial-derived metabolites into the bloodstream is associated with HF progression. A more insightful understanding of the interactions between the human gut microbiome, HF and the associated risk factors is mandatory for optimizing therapeutic strategies based on microbiota modulation and offering individualized treatment.

heart failure gut microbiota metabolites dysbiosis immune modulation

1. Introduction

Heart failure (HF) represents a worldwide health problem with significant associated healthcare costs, morbidity and mortality [1]. It is the final stage that results from cardiac structural and functional damage and subsequent imbalances in the compensatory mechanisms and pathogenic processes [2]. HF can take an acute form, correlated with several inflammatory markers and can also appears as a chronic disease, characterized by an altered inflammatory status associated with pro-inflammatory mediators that are considered essential in HF pathogenesis [3].

The bidirectional communication between gut microbiota and extra-intestinal organs has been intensively studied during the last two decades, leading to a better comprehension of the pathophysiological underlying mechanisms and offering a new characterization of HF clinical features, novel risk factors to be taken into account, new diagnostic tools and new therapeutic options [4][5][6].

2. Gut-Associated Microbiome Composition and Function in Healthy Individuals

The human gut microbiome is considered to be an organ on its own with major interactions within the human organism, playing an active role in various immunological, neuronal, metabolic and endocrine responses [7]. The highest concentration and diversity of microorganisms from the human body lies in the gastrointestinal tract, consisting of more than 500 distinct species of bacteria, viruses, fungi and protozoa [8][9]. The GI microbiota are represented by five primary bacterial phyla: the *Firmicutes* (synonym *Bacillota*) and *Bacteroides* (synonym *Bacteroidota*) phyla predominate the microbiome and represent more than 90% of total bacterial communities, while the *Proteobacteria* (synonym *Pseudomonadota)*, *Actinobacteria* (synonym *Actinomycetota*), and *Verrucomicrobia* phyla are represented in smaller proportions [7][10]. Although the *Bacillota* phylum consists of more than 200 different genera such as *Bacillus*, *Lactobacillus*, *Enterococcus*, *Ruminococcus* and *Clostridium*, and the *Clostridium* genus represents 95% of the phylum. The *Bacteroidota* phylum is predominated by the *Prevotella* and *Bacteroides* genera. The *Actinomycetota* phylum is significantly less abundant than *Bacteroidota* phylum and the *Bifidobacterium* genus is its main representative [11].

The microbiome is not inherited, but acquired, and its composition is changing through different stages of each individual's life, with a unique composition and microbial diversity [12][13]. Its development starts early, in prenatal life, and continues during birth and through senescence [14][15]. The following interfere with microbiome composition, leading the way to health or disease: sex; genetics; the mother's influence during pregnancy and birth; feeding practices in early childhood; dietary habits; antibiotics; tobacco and alcohol use; a sedentary lifestyle associated with the socioeconomic conditions; household pets; pollution; and geographical distribution [9][14][15][16][17].

Whereas each individual's gut microbiota are characterized by a specific combination of bacterial species, due to inter-individual and intra-individual variations throughout human life, the human gut microbiota's functions are highly preserved between individuals [7]. In addition to one's genetic susceptibility, the diversity of the microbiome's composition plays a key role in each individual's personalized response to different environmental exposures such as diet, xenobiotics and medical treatments [2].

The GI mucosa represents the site of the human–external environment interaction. The GI microbiota and the intestinal barrier have bidirectional communication and form a complex network influencing the human state of health and disease [8]. Besides its function as an organ used for digestion and absorption, the GI tract acts as an immune organ, the human body's largest immune organ [18]. "Healthy" gut microbiota have the capacity for: preserving the stability of the intestinal wall and its barrier function; tight epithelial junctions and a normal mucosal immunity; and preventing pathogen proliferation [2]. The gut-associated microbiota can regulate the inflammatory response directly, inducing either innate or adaptive immune responses, or it can alter the immune cells' function using active metabolites, including short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMA-O) and indoleacetic acid (IAA) [19][20][21].

3. Impaired Gut Barrier Function and Inflammation in Heart Failure

The “gut hypothesis” in HF suggests that there is a strong relationship between the gut microbiota, its metabolites and HF pathogenesis, as illustrated in **Figure 1** [2][22]. Although this bidirectional communication is not fully understood, evidence indicates that this bacterial translocation appears in HF as a consequence of various mechanisms leading to structural and functional alterations of the GI tract, from splanchnic congestion to the host’s immunological defense system [23].

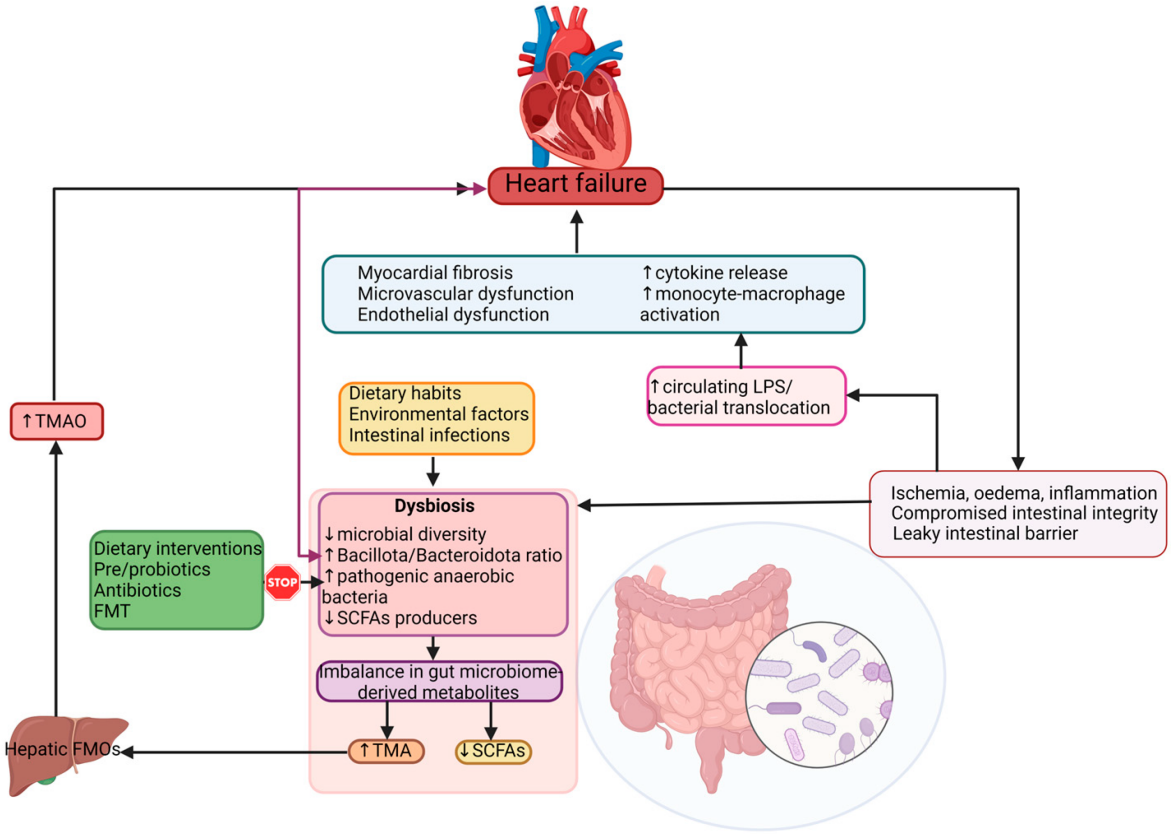

Figure 1. Concept of the gut–heart axis adapted to HF.

Available data suggest that the alteration of the structure and the function of the gut comes as a consequence of the microcirculatory perturbation that appears in HF patients [24]. In these patients, mainly in a decompensated form of the disease, the disruption of the normal composition of the gut microbial communities comes as a result of the intestinal hypoperfusion, that leads to changes in local pH and gut luminal hypoxia [25]. There is evidence of a disrupted intestinal epithelial function associated with HF: an alteration that seems to be the result of a reduced intestinal perfusion and ischemia [13][26].

Besides intestinal wall edema, HF is characterized by a reduction in the absorptive capacity and an increase in the epithelial permeability of the gut, facilitating the passage of several intestinal bacterial and/or endotoxins, such as lipopolysaccharides (LPS), from the gut to the systemic bloodstream [27][28]. LPS is a biologically active constituent of the Gram-negative bacterial wall with potential immunostimulatory activity by using the Toll-like receptor 4

(TLR4) pattern recognition receptor [29]. In HF patients, high LPS concentrations found in the hepatic veins sustain the hypothesis of an intestinal translocation process of gut microbes [30].

The endotoxin intestinal absorption stimulates an increase in systemic inflammatory cytokines levels [13]. According to current data, HF appears to be correlated with a chronic state of inflammation that can be induced or accelerated by this microbial translocation, indirectly affecting cardiomyocytes' normal function [31]. It seems that increased levels of circulating cytokines correspond to more severe clinical symptoms and to a worse prognosis in HF patients' survival [32][33]. Serum levels of TNF-alpha, IL-1 and IL-6 of HF patients are directly influenced by the amount of existing LPSs, currently thought to be leading elements of a hyperinflammatory condition [18]. While in decompensated HF patients, LPS levels appear to be directly associated with systemic inflammation markers, and they decrease following HF recompensation. Treatment administration is not always followed by a decrease in plasma cytokine levels, suggesting a sustained effect as the disease progresses [13][34].

4. Dysbiosis in Heart Failure

Gut microbiota, as the most important active components in the intestinal microecosystem, have been shown to have a strong influence on HF. Besides the correlation with inflammation and increased intestinal permeability, an analysis using fluorescence in situ hybridization described the presence of bacterial overgrowth as mucosal biofilm and an increased bacterial adhesion in the sigmoid colon mucus of HF patients. The increased intestinal juxta mucosal bacterial biofilm has been correlated with an amplified immunoglobulin A–anti-LPS response [13][26].

In stable chronic HF with reduced ejection fraction (HFrEF) patients, an increased level of pathogenic bacteria such as *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* species, as well as yeasts including *Candida* species, have been reported as assessed by microbial culture methods; their levels being correlated with HF severity [35]. Consistent with these results, there is evidence that the *Escherichia*/*Shigella* genus is increased in the same patient known with HF, during its decompensated compared to the compensated phase of disease [36].

Using 16S rRNA gene sequencing Sun and colleagues [37] analyzed fecal samples of patients with severe forms of chronic HF and compared the results with the one obtained from healthy controls. They reported reduced alpha diversity in chronic HF patients and important differences in beta diversity between the two groups. *Bacillota* phylum was found to be dominating the chronic HF patient's fecal microbiota, but in smaller levels than the controls. *Pseudomonadota* and *Actinomycetota*, however, were reported to be more abundant than in the control samples. Moreover, *Pseudomonadota* phylum was the second most abundant phylum found in severe chronic HF patients instead of *Bacteroidota* phylum. *Pseudomonadota* phylum is composed of Gram-negative bacteria, mainly pathogens, and is thought to be a microbial signature of dysbiosis in gut bacterial communities [37].

D. longicatena is a bacterium that produces acetic acid, an SCFA, as a fermentation product. However, acetate can be further used as a substrate in order to generate butyrate [38]. *Eubacterium rectale*, another butyrate producer bacterium, was identified at increased levels in gut mucosal biofilms of HF patients by Sandek and colleagues [26]. In contrast, another study by Kamo et al. [24] reported decreased levels of the bacteria as characterizing HF [24].

Faecalibacterium prausnitzii, another butyrate-producing commensal bacteria with anti-inflammatory properties, was found to be decreased in abundance in HF patients, negatively affecting the intestinal permeability [39][40][41]. Butyrate-producing bacteria are essential for the state of well-being of each individual, as butyrate is used as an energy source for intestinal epithelial cells, and it regulates the integrity of the epithelial barrier and suppresses the intestinal and extra-intestinal inflammation [42][43]. The decreased levels of *F. prausnitzii* and increase in *Ruminococcus gnavus* were found to be important characteristics of gut microbiota in chronic HF patients [44].

5. Risk Factors for HF and Gut Microbiota

5.1. Dietary Choices

The Western diet (WD) is characterized by high sugar and refined carbohydrate intake with a high glycemic index; content that inhibits nitric oxide synthase, resulting in myocardial oxidative dysfunction, cardiac hypertrophy and cardiomyocyte remodeling, all known to be predisposing factors for HF [45]. This diet rich in fast-food aliments and glucose leads to dysbiosis state characterized by elevated *Pseudomonadota* and *Bacillota* levels, which increases the levels of TMAO and ceramides, promotes cholesterol accumulation in macrophages and promotes atherosclerosis development [46]. The WD also leads to lipid accumulation in the myocardium, chronic inflammation and obesity [47]. Increased levels of salt and dietary additives used in fast-food alimentary processing, including nitrites and phosphates, have been associated to an increased risk of HF. They alter the *Bacillota* to *Bacteroidota* ratio [48].

5.2. Obesity

Savji and colleagues [49] in their study reported that obesity and its associated dysmetabolism, including hyperlipidemia, hyperglycemia and insulin resistance, are strongly correlated with HF [49]. A pro-inflammatory environment characterized by elevated levels of pro-inflammatory cytokines is promoted by obesity and its associated cardiometabolic factors (insulin resistance, dyslipidemia and abdominal adiposity) [50]. The endothelial dysfunction and the nitric oxide unavailability might lead to left ventricular hypertrophy and systolic and diastolic dysfunction in HFpEF [50][51].

5.3. Type II Diabetes Mellitus

Type II diabetes mellitus (T2DM) is a strongly associated risk factor for HF and other CVD. Patients known to have T2DM present a decreased level of bacterial genera such as *Faecalibacterium*, *Bifidobacterium*, *Akkermansia*, *Bacteroides* and *Roseburia. Roseburia*, *Bacteroides* and *Akkermansia* have anti-inflammatory effects. *Bacteroides* and *Akkermansia* in decreased levels lead to an under expression of tight junctions' genes, elevated "leaky gut", and, in consequence, endotoxemia [52].

5.4. Hypertension

Persistently elevated blood pressure (BP) patients present a higher (up to five-fold) *Bacillota*-to-*Bacteroidota* ratio in comparison to normotensive controls [53]. Moreover, the intestinal microbiota is dominated by lactate-producing genera (e.g., *Turicibacter* and *Streptococcus*), while SCFA-producing ones appear to be reduced (such as *Clostridiaceae*, *Bacteroides and Akkermansia*) when hypertension is present [54][55]. Some of these associated perturbations in gut microbiota homeostasis are partially related to HF pathogenesis and increase the risk of HF progression.

6. Gut-Derived Metabolites as Possible Biomarkers Related to Intestinal Dysbiosis in HF

A biomarker is defined as a biological compound that is easily accessible and measurable in the body. Biomarkers can be classified as molecular, cellular or imaging. Their role is to help in identifying the disease or provide therapeutic guidance. Natriuretic Peptides (NP), brain-type natriuretic peptide (BNP), N-terminal prohormone of BNP and cardiac troponin measurements—classic HF biomarkers—have already been included in the guidelines for HF diagnosis and treatment by the European Society of Cardiology (ESC) [56] and the American Heart Association (AHA) [57]. The addition of other diagnostic and prognostic biomarkers that could be associated to such a complex disease would be of benefit for both patients and medical practitioners.

Gut microbial-derived metabolites can also play a significant role in the pathogenesis of HF. It appears that the gut microbiome acts similarly to an endocrine organ. By generating active biometabolites including short-chain fatty acids (SCFAs), trimethylamine (TMA)/trimethylamine N-oxide (TMAO), and bile acids, the gut microbiome influences the host physiology. Several studies described the association of the gut's microbiome metabolites and different pathologies including hypertension, atherosclerosis, HF, obesity, chronic kidney disease, and T2DM [2][23][58][59][60][61]. These metabolites can be considered as biomarkers of intestinal dysbiosis and can predict inflammation in patients known with HF [61]. These patients with elevated plasma levels of phenylalanine display increased levels of inflammatory cytokines (IL-8, IL-10), C-reactive protein (CRP) and associate higher mortality [62], whereas glycine manifest anti-inflammatory effects and seem to offer protection to the cells and heart [63].

Alterations of gut microbiota composition, especially elevated N-oxidetrimethylamine (TMAO) levels are correlated with the risk of developing HF [64]. TMAO is a metabolite produced by gut bacteria including *Bacillota* and *Pseudomonadota*, obtained from choline, phosphatidylcholine, and L-carnitine fermentation [2]. Chen and colleagues [64] reported that an elevated level of TMAO resulted from a diet high in saturated fat and sugar can lead to fibrosis, myocardial inflammation and to impaired diastolic function [64]. Individuals with an increased abundance of *Ruminococcus*, *Prevotella* and *Clostridium* genera and the *Lachnospiraceae* family, and decreased levels of *Bacteroidota*, revealed higher levels of TMAO in their plasma [65][66]. HF–associated dysbiosis is characterized by high levels of circulating TMAO, that are able to stimulate cardiac remodeling through promoting myocardial fibrosis and pro-inflammatory effects [2][45][67][68].

HF patients display elevated plasma levels of TMAO when compared to healthy individuals. Increased TMAO levels can be used as a prognostic biomarker in both acute and chronic HF, independently of B-type natriuretic

peptide (BNP) and traditional risk factors, as TMAO levels are predictive of an augmented risk of mortality in these patients [48][49]. Elevated TMAO plasma values correspond with advanced stages of left ventricular diastolic dysfunction [48]. TMAO can also be considered a prognostic predictor of HFeEF and a marker of risk stratification for this particular category of patients [69][70].

The SCFAs are represented by acetate, propionate and butyrate, and they are generated by gut bacteria including *Bacteroides*, *Bifidobacterium* and *Faecalibacterium* spp. [71]. They are the most important metabolites produced through colon bacteria fermentation of resistant starch and dietary fibers [61]. Most evidence sustains the fact that SCFAs have a protective role against HF and play a major role in maintaining the integrity of the intestinal barrier: in mucus production and they are active in anti-inflammation protection [72].

7. Interactions between the Gut Microbiome and Cardiovascular Drugs

Age, sex, nutritional status, disease states, along with genetic and environmental exposures are factors that can explain how individuals will respond to drug therapies [73]. The human microbiome is known for its involvement in drug metabolism and pharmacological efficacy, but among them there is bidirectional communication, as drugs can also influence microbiota composition.

Drug absorption is an elaborate process, depending on many factors such as their solubility and stability in GI fluids, their pH, GI transit period, permeability through epithelial membranes and the drugs' interaction with the host and microbial enzymes [74]. The human gut microbiota is genetically capable of producing enzymes involved in oral drugs' metabolism, facilitating their absorption across the gut and through the bloodstream [73]. Dysbiosis of the gut's bacterial communities can further alter drug pharmacokinetics; the activation of prodrugs can contribute to the production of unwanted toxic metabolites and the inactivation of drugs [75]. Variation in drug response can also be present in a "healthy" gut, due to inter-individual differences in intestinal bacterial species [7].

Related to the cardiovascular medication used in HF patients, metagenomic sequencing of stool samples from HF patients revealed that the use of several pharmaceutical agents such as statins, beta-blockers, angiotensin-converting enzyme inhibitors and platelet aggregation inhibitors has an important influence on gut microbial composition [76]. Despite the fact that specific underlying mechanisms are unknown, partial results of the study were reproduced by another British group of researchers [77].

7.1. Cardiac Glycosides

Digoxin, a drug frequently recommended in HF is a good example of microbiota influencing drug bioavailability. Some strains of *Eggerthella lenta* are responsible for converting digoxin into an inactive microbial metabolite, limiting the quantity of active drug absorbed into the systemic bloodstream in an important 10 percent of patients [78][79].

7.2. Blood Thinners and Gut Microbiota

Aspirin is a non-steroidal anti-inflammatory drug (NSAIDS) commonly used to decrease the risk of cerebrovascular and cardiovascular disorders [79]. Existing evidence demonstrates its ability to disrupt the gut's microbiota composition. Patients using aspirin present variations of *Ruminococcaceae*, *Prevotella*, *Barnesiella* and *Bacteroides* bacterial levels in comparison to individuals not using or using other types of NSAIDs. Furthermore, the gut's bacterial communities' composition seems to exert influence on aspirin metabolism. While oral antibiotic administration can decrease the gut microbiota's metabolic activity by slowing its degradation, increasing its bioavailability and prolonging its anti-thrombotic action, probiotics containing *Bifidobacterium breve* Bif195 bacteria can protect against an aspirin intake adverse reaction, such as intestinal wall damage and aspirin-induced gastric ulcers [80][81].

7.3. The Effects of Beta-Blockers, ACEi, and ARBs on Gut Microbiota

The effects of antihypertensive medications have been investigated on several occasions, both in animal and human studies. Despite expectations, the association between the use of beta-blockers, angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACE inhibitors) can modify the composition of gut microbiota.

7.4. Statins and Gut Microbiota

Statins are drugs used for their capacity to decrease low-density-lipoprotein-C (LDL-C) and cholesterol levels. Inter-individual variations in the response to statin treatment are well-known, and are not related to a specific statin agent or dose [76]. Studies have proven their action on modulating gut bacterial communities' composition [73][82]. Individuals treated with atorvastatin presented an increased level of anti-inflammatory gut bacteria such as *Faecalibacterium prausnitzii* and *Akermansia muciniphila*, whereas untreated patients known with hypercholesterolemia displayed an increased level of bacterial species with pro-inflammatory effects, such as *Collinsella* and *Streptococcus* [83]. LDL-C levels seem to be negatively correlated to the phyla *Bacillota* and *Fusobacteria*, while *Lentisphaerae* and *Cyanobacteria* spp. were positively associated with LDL-C [82].

8. Modulation of Dysbiosis as a Potential Target in Heart Failure

Considering that dysbiosis is a key factor in HF pathogenesis and disease progression, targeting the disrupted gut microbiota could be considered an effective therapeutic objective. The possibility of characterizing each patient's gut microbiota and his disease-associated dysbiosis allows the initiation of a personalized, targeted therapeutic plan. Although there are various ways to manage and modulate the dysbiotic intestinal microbiota, such as dietary interventions (which also include the use of prebiotics, prebiotics and postbiotics) and fecal transplantation, several reports from the available literature place diet modification and probiotic use as the main interventions for microbiota modulation.

Diet has always been considered a crucial factor in shaping the structure and function of gut's associated microbiota. A 5-day adjusted diet has been shown to produce beneficial changes in the number and species of the gut microbiota [84]. Often cited in the medical literature, the Mediterranean diet (MD) consists of elevated levels of polyunsaturated fatty acids, dietary fiber, polyphenols, and a small quantity of red meat [45]. Among its recognized benefits on human health, an MD provides an increased abundance of probiotics, greater biodiversity, elevated SCFAs, and reduced TMAO [85][86]. Adherence to an MD was associated with a decreasing HF incidence up to 74% [87].

A high-fiber diet has recently been demonstrated to improve gut dysbiosis (described by the *Bacilliota* and *Bacteroidota* ratio), reduced blood pressure, improved cardiac function and normalized cardiac hypertrophy in a hypertension-induced HF experimental model [88]. Additionally, fermentation of fiber results in augmented SCFA production, with their beneficial actions on human health [89].

Related to antibiotic use in modulating the gut microbiota in HF patients, results are controversial. In animal models, oral vancomycin use induced smaller left ventricular infarct size, and improved recovery cardiac function following ischemia/reperfusion experiments in treated, compared to untreated, rats [90]. Rifamixin, besides its bactericidal and bacteriostatic effect, also has the capacity to reduce translocation of bacteria and toxicity, has an anti-inflammatory effect and can positively regulate the composition of the intestinal microbiota, promoting the growth of *lactobacillus* and bifidobacteria [91][92]. As for human clinical trials, the results are contradictory. The use of a cocktail of tobramicyn and polymixin B, in HF patients, normalized the level of intestinal Gram-negative bacilli, significantly decreased pro-inflammatory cytokines and improved flow-mediated dilation: evidence of endothelial dysfunction [93].

Prebiotics are "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health" [94]. Prebiotics use could increase the amount of *Bifidobacterium* and promotes a higher body weight loss, which decreased systolic and diastolic blood pressure [95].

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