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The Role of Gut Microbiota Dysbiosis on the Pathogenesis of Cardiovascular Diseases: A Review

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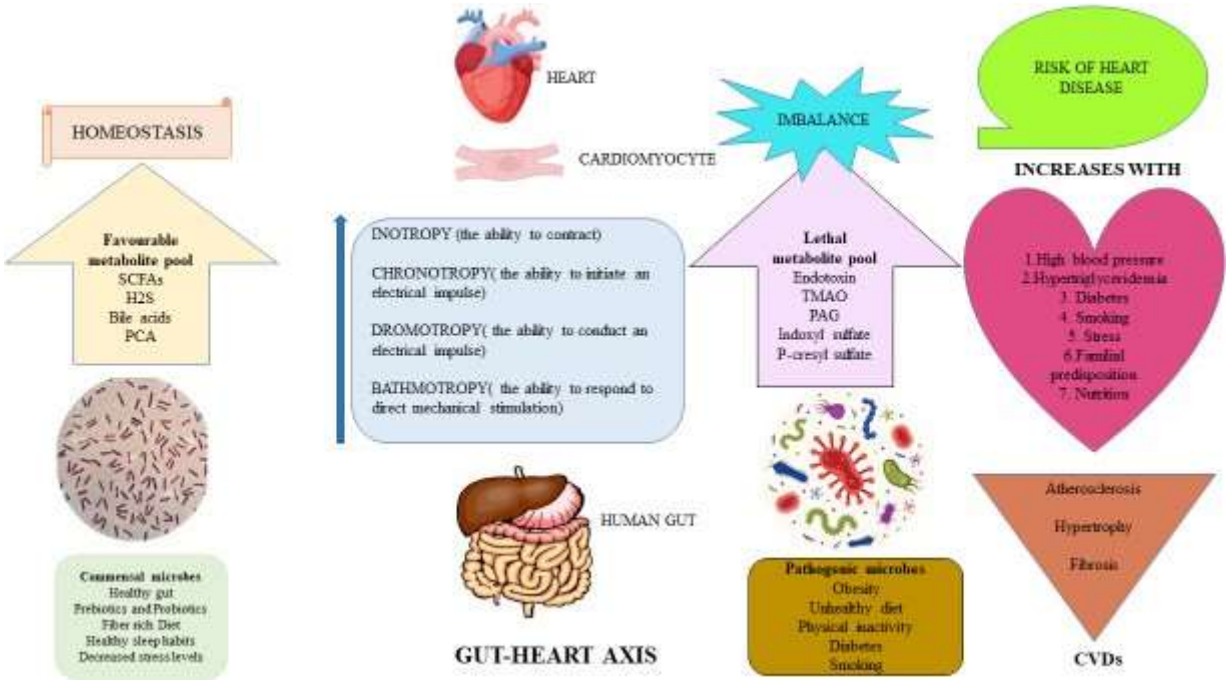
Abstract

The regulation of human physiology is greatly influenced by interactions between the intestinal microbiota and the host. Gut dysbiosis, or harmful changes to the gut microbiota, has been associated with the onset and progression of several illnesses, including cardiovascular disease (CVD). In the entire world, cardiovascular disease (CVD) is the main cause of death. The regulation of the host's metabolism and energy-harvesting mechanism is largely dependent on the gut bacteria. Changes in the gut microbiota derived metabolites and variations in the microbial flora have been demonstrated to significantly correlate with a number of CVD risk factors. Below is a detailed discussion of the function of gut microbial dysbiosis in dyslipidemia, atherosclerosis and coronary artery disease (CAD), hypertension, chronic heart failure (CHF), even myocardial infarction, and related treatment implications. However, there are even more, such as dietary changes, probiotics, and prebiotics, which may one day be utilised to process the microbial population and change its functional output for the benefit of the host. With a focus on the intricate interactions between microbiota, their metabolites, and cardiovascular disease (CVD), this review will cover the roles of gut microbiota in healthy physiology, their associations with disease settings, and the possibility of modulating gut microbiota as novel therapeutic targets.

Keywords: Microbiota, dysbiosis, cardiovascular diseases, pre and probiotics, therapeutic



Graphical Abstract: Gut- Heart Axis. Abbreviations used: SCFAs= Short chain fatty acids, H_2S=Hydrogen sulphide, PCA= Protocatechuic acid, TMAO=Trimethylamine N-Oxide, PAG= Phosphate activated glutaminase

Introduction

The Human body is home to a variety of microbiotas or microbiomes. Microbiome is mainly the collective genomes of the micro-organisms in a particular environment, and microbiota is the community of micro-organisms themselves [1]. The human gastrointestinal tract is divided into compartments that consist of various complicated regions, ranging from the oesophagus to the rectum. The physiochemical characteristics such as transit rates of the luminal content, local pH, redox potential, availability of diet-derived compounds, and host secretions (e.g., hydrochloric acid, digestive enzymes, bile, and mucus) vary in each of the regions of GI tract [2]. Hence the composition, quantity and functionality also vary throughout the sections of the GI tract. The normally dominant phyla are Firmicutes and Bacteroidetes, which account for 90% of bacterial species inhabiting the human gut [3]. The diverse community of gut microbiota in the GI tract forms a symbolic cooperation with the human host. The majority of the microbiota belongs to the phyla Firmicutes (*51%) including the Clostridium coccoides and Clostridium leptum groups and the well-known Lactobacillus genera and the phyla Bacteroidetes (*48%) including the well- known genera Bacteroides and Prevotella [4]. The remaining 1% consists of other less populous phyla, including Proteobacteria, Actinobacteria (including the Bifidobacteria genera), Fusobacteria, Spirochaetes, Verrucomicrobia and Lentisphaerae [5]. From the neonatal period onwards, the gut microbiota determines the formation of the intestinal architecture [6]. Several studies proved that gut microbiota is essential for maintaining intestinal health and giving protection against pathogenic invaders, thus some investigators have referred to it as an “extra organ” of the host [7]. The microbiota provides a fundamental influence on systemic immunity and metabolism, and specifically, healthy gut microbiota is largely responsible for the overall health of the host [8]

Cardiovascular disease (CVD) is literally a disease of the heart and blood vessels and includes all diseases that affect the heart and circulatory system of the body, e.g. coronary heart disease, angina, hypertension,

stroke and peripheral vascular disease (PVD - any disease or disorder of the circulatory system outside of the brain and heart). [9]. Atherosclerosis (and thrombosis), cerebrovascular disease, hypertension, heart failure, atrial fibrillation, and myocardial fibrosis are some pathological cardiac-related diseases that hamper human lives daily [10]. The most well-known and extensively studied CVDs are Chronic Heart Disease (CHD) and stroke. As the leading cause of mortality at the global level, CVD contributes to 30% of all deaths across the world [11]. The number of CVD-affected people increased from 271 million in 1990 to 523 million in 2019, and deaths due to CVD climbed significantly from 12.1 million in 1990 to 18.6 million in 2019 [12] According to a 2022 American Heart Association report, an estimated 19 million CVD-related deaths occurred globally, with three-quarters of these deaths occurring in low-and middle-income countries (LMICs) [13]

This review article primarily focuses on addressing the tight linkage between the gut microbiome and the cardiovascular system.

Homeostasis of Microbiota

According to one definition of intestinal homeostasis (also known as eubiosis), it is "the natural tendency to achieve relative balance, each internal and behavioral chemical-physical residences, which unites all residing organisms, for which this dynamic regime should be maintained over the years, although it adjusts outside situations, through special self-regulatory mechanisms" [14] Dysbiosis negatively affects the homeostasis of microbes and their hosts [15].

The structure of the intestine and cardiovascular disease

The systemic circulation of the cardiovascular system is probably the closest neighbor to the gastrointestinal tract, gut microbiome and its components across the intestinal barrier. This close distance increases the sensitivity between the two systems and any imbalance in the GI tract affects the cardiovascular system [16]. In the progression of cardiovascular pathogenesis, multiple crucial contributors are sequentially present, including the gut microbiome, intestinal permeability, gut-derived substances (e.g. metabolites, toxins, and peptides), immune system and the cellular components of the cardiovascular system [17].

The increased intestinal permeability, termed as 'leaky', leads to loose tight junctions between adjacent epithelial cells and a damaged intestinal mucus layer [18]. In this situation, antigens, bacteria, endotoxins, and toxins from the lumen would constantly enter the systemic circulation [19]. This leaky gut accelerates the progression of dysbiosis-related cardiovascular diseases by facilitating endotoxin influx, resulting in alterations in the metabolite and cytokine pools in the host systemic circulation [20]. Sensors, such as TLRs and receptors for advanced glycation end products (RAGE) recognized endotoxins [21]. They in turn increase the production of cytokines (e.g. TNFα, interleukin (IL)-1β, IL-6 and IFNγ) [22]. Elevated cytokine levels trigger arterial inflammation, the accelerating factor of many cardiovascular complications (e.g. atherosclerosis, hypertension and CHD) [23].

Endothelium and Cardiovascular disease

The circulatory system has a basic structure and consists of three different layers: the tunica intima constitutes endothelium supported by a basement membrane and delicate collagenous tissue, the tunica media- an intermediate muscular layer and an outer supporting tissue layer called the tunica adventitia [24]. Endothelial cells play important roles in the modulation of vascular tone, and the clustering of substances

between circulation and underlying vascular cells [25] Dysfunction of endothelial cells is a predisposing factor of the development of both cardiac and vascular complications, particularly atherosclerotic cardiovascular disease [26]. When the intestinal barrier is damaged, the endothelial cells are exposed to endotoxin, cytokines and gut- derived metabolites, and are therefore prone to endothelial dysfunction [20]. The association between inflammatory cytokines and endothelial dysfunction influence the underlying mechanisms of many cardiovascular diseases [27].

Are gut and Heart diseases connected?

Heart Failure- Heart failure is a serious condition in which the heart is unable to pump enough blood to meet the needs of the body [28]. Heart failure patients develop reduced cardiac output, increased tissue congestion, and peripheral vasoconstriction [29]. In this disease, intestinal villi or microvilli undergo ischemia and are susceptible to anorexia [30]. It is observed that the structure and function of the gut are fundamentally altered in patients with HF [31]. Structurally the patients have thickened walls of the terminal ileum and colon, which indicates bowel edema and increased collagen accumulation in the mucosal layer of the small intestine. Imbalance in the intestinal microcirculation and altered function of the intestinal barrier may provoke cytokine production that in turn contributes to impaired cardiac function [32]. Levine B. et al also claimed that circulating levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) have been increased in patients with acute decompensated HF [33]. The simultaneous changes in intestinal microbiota and metabolome in a mouse model of pressure overload demonstrated that intestinal microbiota and the associated metabolites were significantly altered in mice with HF. These findings are the first line of evidence showing the direct impact of HF on gut dysbiosis and associated microbial metabolites [34]. Pasini et al. conducted a study on 30 well-nourished patients in stable condition with mild CHF and 30 with moderate to severe CHF and concluded that Pathogenic gut flora overgrowth was present in most patients with CHF [35].

Atherosclerosis- Atherosclerosis is a complication that is characterized by the accumulation of lipids, fibrous elements, and calcification within the large arteries. This mechanism is begun by endothelium activation, followed by a series of events, which constitutes the vessel narrowing and activation of inflammatory pathways leading to atheroma plaque formation [36]. The primary mechanism of the gut-heart axis conducted atherosclerosis is mainly acceleration of butyrate, trimethylamine-N-oxide (TMAO), endotoxin (LPS) and phenyl acetyl glutamine (PAGln) produced by the bacteria [37]. TMAO plays a prominent role in atherosclerotic plaque advancement, exacerbating the vascular wall's inflammatory reactions, promoting reactive oxygen species production, and inhibiting cholesterol reverse transport [38]. Microbiota could reach the atherosclerotic plaque is phagocytosis by macrophages at epithelial linings. Then, the activated macrophages reach the activated endothelium of the atheroma, and the atheroma enters the bloodstream to transform into cholesterol-laden foam cells [39]. Gut microbiome composition happened to be more inflammatory in atherosclerotic patients. The gut microbiota profile of atherosclerotic patients includes a higher abundance of *Escherichia coli*, *Klebsiella* spp., *Enterobacter aerogenes*, *Streptococcus* spp., *Lactobacillus salivarius*, *Solobacterium moorei*, and *Atopobium parvulum,* whereas depletion of gut species such of *Bacteroides* spp., *Prevotella copri*, and *Alistipes shahii* [40].

Hypertension- Hypertension, the most significant threat to global morbidity and mortality, serves as a major risk factor causing cardiovascular diseases [41]. Many studies confirmed the associations between gut microbiome composition and BP regulation [42]. One mechanism is the production of Short chain fatty acids (SCFA) by the gut microbiota thereby activation of two orphan G protein-coupled receptors, GPR41

(aka Free Fatty Acid Receptor 3), GPR43 (aka Free Fatty Acid Receptor 2), and olfactory receptor 78 (Olfr78). The increase in blood pressure caused by SCFA-induced renin release from the afferent arteriole is mediated by Olfr78 [43]. GPR41 and GPR43 are activated when they bind to acetate, propionate and butyrate [44] Natarajan et al. added propionate to the diet of GPR41−/− and GPR41+/− mice and observed after GPR41 knockout, mice exhibited thickening of the aorta and increase in vascular collagen, consequently causing vascular fibrosis and hypertension [45]. Sun et al. examined cross-sectional associations between gut microbial diversity and taxonomic composition and BP in 529 middle-aged adults in the CARDIA Study (Coronary Artery Risk Development in Young Adults) and found that within-person diversity of the gut microbiota is inversely associated with hypertension and systolic BP (SBP) [46]. In the presence of hypertension, the intestinal microbiota is dominated by lactate- producing genera (e.g., Streptococcus and Turicibacter), while short chain-fatty-acid-producing ones appear to be reduced (such as Akkermansia, Bacteroides, and Clostridiaceae) [47].

Hypercholesterolemia- High serum cholesterol, known as hypercholesterolemia, is a long-term contributor factor to CVD. The deposition of cholesterol in the arterial wall creates plaques that can lead to atherosclerosis [48]. In the small intestine, certain gut microbes produce an enzyme known as bile salt hydrolase (BSH) capable of deconjugating (i.e., removing glycine or taurine conjugates) bile acids preventing their reuptake by the Apical Sodium Dependent Bile Acid Transporter (ASBT transporters). BSH genes have been detected in Gram-positive gut bacteria including *Lactobacillus*, *Clostridium*, *Listeria*, and *Bifidobacterium* [49]. Primary Bile Acids can be further metabolized through gut microbial 7α-dehydroxylation to secondary Bile Acid known as lithocholic acid (from chenodeoxycholic acid) and deoxycholic acid (from cholic acid) [50]. In gut dysbiosis, there may be a reduction in the level of secondary bile acids, leading to an abnormal accumulation of primary bile acids, and downregulation of the bile acid production mechanism (FXR–TGR5 pathway) [51].

Myocardial Infarction- Myocardial Infarction (MI) is necrosis occurring from acute obstruction of a coronary artery. MI affects predominantly the left ventricle (LV), but the damage may extend into the right ventricle (RV) or the atria [52]. MI episodes are allegedly associated with a sequential change in the gut-brain axis, which substantially alters the gut microbiome (dysbiosis) [53]. It was observed by Benakis. C et al. that dysbiosis suppresses the effector T cells trafficking from the gut to the leptomeninges after a stroke by increasing regulatory T cells and reducing IL-17+ γδ T cells through altered dendritic cell activity this results in increased chemokine production in the brain parenchyma and subsequent infiltration of cytotoxic immune cells, including neutrophils [54]. IL-17 expression in atherosclerotic lesions, is associated with increased plaque vulnerability, a known risk factor for embolic stroke [55]. To understand the composition of gut microbiota in stroke patients Han et al. conducted a study on 30 AMI patients and 30 healthy controls and found that gut microflora in AMI patients contained a lower level of the phylum *Firmicutes* and a slightly higher abundance of the phylum *Bacteroidetes* compared to the healthy controls. The AMI group was also identified by higher levels of the genera *Megasphaera*, *Butyricimonas*, *Acidaminococcus*, and *Desulfovibrio*, and lower levels of *Tyzzerella 3*, *Dialister*, *[Eubacterium] ventriosum group*, *Pseudobutyrivibrio*, and *Lachnospiraceae ND3007 group* as compared to that in the healthy controls [56].

Effects of metabolites on the Cardiovascular disease

Trimethylamine N-oxide (TMAO) - Trimethylamine N-oxide (TMAO) is a metabolite that is derived from gut microbiota, and is converted from trimethylamine by the liver enzyme flavin monooxygenase 3

(FMO3) [57]. Choline, L-carnitine, betaine, and other choline-containing compounds are the major nutrient precursors of gut microbe-dependent TMAO [58]. L-carnitine and choline are mainly present in animal-origin foods, such as meat (especially red meat), meat products, eggs, and shellfish, while betaine is found mostly in plants [59]. Many studies proved that TMAO may be associated with the pathogenesis of CAD and the risk of CVDs [60]. TMAO is considered a biomarker of cardiovascular complications, promoting the dysfunction of endothelial cells, Vascular Smooth Muscle Cells (VSMCs) and cardiomyocytes. Studies have confirmed that TMAO plays an important role in inducing foam cell formation and vascular inflammation by up-regulating the MAPK/JNK pathway and MAPK/ERK pathway [61]. Subsequent preclinical experiments show that TMAO may directly affect the heart by inducing myocardial hypertrophy and fibrosis, endothelial cell and vascular inflammation, as well as cardiac mitochondrial dysfunction, thereby aggravating the progress of Heart Failure [62]. Increased TMAO levels induced the activation of the NF-kappa B (NF-κB) pathway and increased the expression of pro-inflammatory genes including inflammatory cytokines, adhesion molecules and chemokines [63]. TMAO levels were significantly correlated with the percentage of pro- inflammatory intermediate CD14++CD16+ monocytes in ischemic stroke patients [64].

Short Chain Fatty Acids- SCFAs have structurally less than six carbons and are considerable products of diet digestion and fermentation of dietary fibers in the intestine. In the gut, the microbiota convers dietary fiber into monosaccharides through several key events mediated by the enzymatic reactions of specific gut microbiota. Major end products from these fermentations are the SCFAs [65]. The main short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate, are absorbed into the systemic circulation and can act as hormone signals on target tissues/cells [66]. Brandsma, E. et al. stated that the decrease in SCFA-producing microbiota in *Casp1*−/− mice leads to the reduction in microbiota-derived anti-inflammatory SCFAs (propionate, acetate, and butyrate) in the cecum to accelerate inflammation and atherogenesis [67]. Propionate is generated from the metabolism of branched-chain amino acids (BCAAs) and intestinal bacteria and has beneficial properties by diminishing CVD progression [68]. The functions of propionate in the cardiovascular system may be contributed by protein propionylation and histone lysine propionylation [69]. Propionylation of histone H3Lys14 (H3K14pr) is predominantly enriched at the promoters of the highly transcriptionally activated genes required for Fatty Acid oxidation, and is associated with cardiovascular physiological and pathological progress [70]. Malonate, the three-carbon dicarboxylic acid, participates in CVDs directly or indirectly. Stress-induced CVDs are predominantly affected by oxidative stress. Mitochondrial ROS contributes to endothelial dysfunction and hypertension, whereas malonate could attenuate mitochondrial ROS production in Ang II-induced hypertension [71]. Malonate and Lysine malonylation (Kmal) of non-histone proteins are critically involved in CVDs, such as angiogenic defect, cardiac hypertrophy, and myocardial infraction, by regulating the malonylation within the myocytes and endothelial Cells [68]. Butyrate is another SCFA, mainly produced in the gut, and the concentration of butyrate in the blood passing from the intestinal tract to the liver, heart, and lungs mimics the production rate in the large intestine. [72]. Butyrate improves cardiac function and suppresses myocardial remodeling in the diabetic heart via inhibiting histone deacetylase (HDAC) activity and enhancing the expression of superoxide dismutase (SOD1) [73]. Hyperproliferation of VSMCs is a hallmark of atherosclerosis and arterial aneurysms. Butyrate inhibits the proliferation of VSMCs by promoting the anti-oxidative effect and anti-inflammatory response [74].

Therapeutic Intervention by probiotic and prebiotic

Probiotics and prebiotics playing affirmative roles in altering the microbial and metabolic composition of gut microbiota could be regarded as a potential therapeutic intervention for CVD [75]. The most widely accepted definition of this term is reaffirmed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) as a substrate that is selectively utilized by host microorganisms conferring a health benefit [76].

The Food and Agriculture Organization of the United Nations-World Health Organization (FAO-WHO) officially defined probiotics as: "live microorganisms that when administered in adequate amounts confer a significant health benefit on the host" [77]. Probiotics contain a set of beneficial microorganisms. Most of these belong to lactic acid bacteria, such as Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus, and Enterococcus. The yeast genus Saccharomyces is also one of the well-known probiotics [78]. Core probiotic genera such as Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, and Enterococcus have been found to improve several CVD risk factors [79]. The protective effects of probiotic and prebiotic therapies on CVD could also be explained by the modulation of the host immune system. The immunological mechanisms of probiotics and prebiotics involve the alterations of dendritic cells, epithelial cells, T regulatory cells, effector lymphocytes, natural killer T cells, and B cells [80]. Human studies with probiotic strains show that ingestion of viable microorganisms shows the ability to hydrolyze bile salts to lower blood cholesterol, alleviating a risk factor for CVD [81]. Treatments with different probiotic strains on CVD patients or animals may rebalance bacteria composition and their metabolites in the gut by directly interacting with other beneficial bacteria and competing against harmful microorganisms, or indirectly helping/inhibiting the production of gut-derived metabolites, thereby affecting the downstream inflammatory responses or gene expressions in end- organs of the host [75]. Lactobacillus spp., which is a well-established lactic-acid-producing probiotic bacteria carry anti-inflammatory and cholesterol-lowering effects [82]. Many mice experiments proved that Lactobacillus acidophilus, Lactobacillus reuteri, and several strains of Lactobacillus plantarum have cardioprotective effects mitigating doxorubicin-induced cardiomyopathy [83]. The use of Lactobacillus plantarum strains might serve a dual role when protecting the heart, first by exerting beneficial effects of its own, and second, by enriching other likely beneficial bacteria, e.g., Lachnospiraceae_NK4A136_group. [84]. In animal experiments, administration of the probiotic strains *Lactobacillus plantarum* ZDY04 (85) and *Enterobacter aerogenes* ZDY01 (86) markedly decreased choline-induced cecal TMA and serum TMAO levels by remodeling the gut microbiota in mice. The exopolysaccharide-producing probiotic *Lactobacilli mucosae* DPC 6426 ameliorated atherosclerosis by reducing serum cholesterol and altering the relative abundance of enteric Microbiota [87]. Supplementation of probiotic *L. mucosae* A1 exhibited effectiveness in the treatment of hyperlipidemia and atherosclerosis and improved gut microbiota dysbiosis, including increased richness and diversity in ApoE -/- mice on a Western diet [88]. In a study done by Raygan F. et al., 60 diabetic patients with CHD, aged 40–85 years were selected for evaluating the effects of probiotic supplementation on cardiovascular disease. After the 12-week intervention, probiotic supplementation significantly decreased fasting plasma glucose, insulin resistance, and total-/HDL-cholesterol ratio and significantly increased insulin sensitivity HDL-cholesterol levels. [89]. A meta-analysis by Shimizu et al. including 11 randomized controlled trials, found that probiotic supplementation could be useful in the treatment of hypercholesterolemia as they observed a reduction of TC and LDL [90].

There are several selection criteria for prebiotics, which are (1) resistance to digestion in the upper sections of the alimentary tract, (2) selective fermentation by potentially beneficial microbiota in the colon, (3)

beneficial effect on host health, (4) selective stimulation of growth of probiotics, and (5) stability in various food/feed processing conditions [91]. Prebiotics present in natural products or added to food could be fermented by gut bacteria and thus affect the structure of gut bacteria composition and metabolic activity [92]. Oligosaccharides, especially fructans (fructooligosaccharides (FOS) and inulin) and galactans (galactooligosaccharides (GOS)), are the well-known prebiotics, as evidenced by in vitro and in vivo studies. Dietary fiber is also nonfermentable by human digestive enzymes and is sometimes used interchangeably with prebiotics [93]. Prebiotics modulate the gut microbiota exerting an inverse correlation with the risk of cardiometabolic diseases [94]. Supplementation with inulin (or co-supplementation with inulin and other components) reduced the levels of cholesterol, including total and LDL cholesterol, CRP, and several inflammatory cytokines. It improved anti-oxidative parameters and gut microbiota dysbiosis [95]. The administration of a prebiotic complex based on fermented wheat bran was observed to correct intestinal dysbiosis and endotoxemia in female rats with heart failure [96]. Chitosan oligosaccharides (COS) a prebiotic, exhibited protective effects in CHD by ameliorating antioxidant capacities and lipid profiles through promoting the growth of probiotic species in intestinal flora [97]. Parnell and Reiner reported that prebiotic intake lowered total serum cholesterol in a hypercholesterolemic rat model. During this research, rats were administered one of three diets with 0, 10, or 20% prebiotic fiber for 10 weeks. Both doses of prebiotic fiber reduced serum cholesterol concentrations by about 25% [98].

Discussion

One of the most significant interfaces (250–400 m2) between the host, external stimuli, and internal antigens is the human gastrointestinal (GI) tract [99]. The collection of bacteria, archaea and eukarya colonizing the GI tract is termed the ‘gut microbiota’ [100]. The intestinal microbiome plays an important role in controlling whole-body metabolic homeostasis and organ physiology [101]. Any imbalance between the host and pathogenic microbes, termed dysbiosis, threatens the host's health [102].

Cardiovascular disease (CVD) is a major increasing factor of mortality throughout the world. The underlying pathology is the construction of plaque, which develops over many years and is usually advanced by the time symptoms occur, generally in middle age.

Gut Microbiota performs a key role in gut-heart axis during CVD progression. Altered microbiota composition has a significant effect on CVD risk leading to atherosclerotic plaque build-up in arteries [103]. The “gut hypothesis of heart failure” implies that reduced cardiac output caused by heart failure can lead to decreased intestinal perfusion, mucosal ischemia, and then intestinal mucosal destruction [104]. In the development of atherosclerosis, there is an alteration in lipid metabolism which is affected by gut microbiota [105]. Gut microbiota dysbiosis was observed in hypertension, including decreased diversity, altered microbial structure, composition change of taxa, alterations of microbial function, nutritional and immunological factors, and microbial interactions [106]. Many shreds of evidence suggest that gut microbiota may have systemic effects on the host by producing bioactive metabolites, such as short-chain fatty acids, bile acids, and TMAO [107].

The role of gut microbiota in human health and well-being is being widely studied in various aspects (Figure2). Probiotics and prebiotics playing positive roles in altering the microbial and metabolic composition of gut microbiota could be regarded as a potential therapeutic tactic for CVD [75]. The probiotic treatment prevents CVD by restoration of gut microbiota dysbiosis and anti-inflammatory responses by reducing oxidative stress, lowering hypercholesterolemia, and lowering high blood pressure [108]. Through various explanations of the mechanism of prebiotics, it is explained that prebiotics has a

beneficial effect on the prevention of CVD by modulating gut microbiota and inflammatory responses.

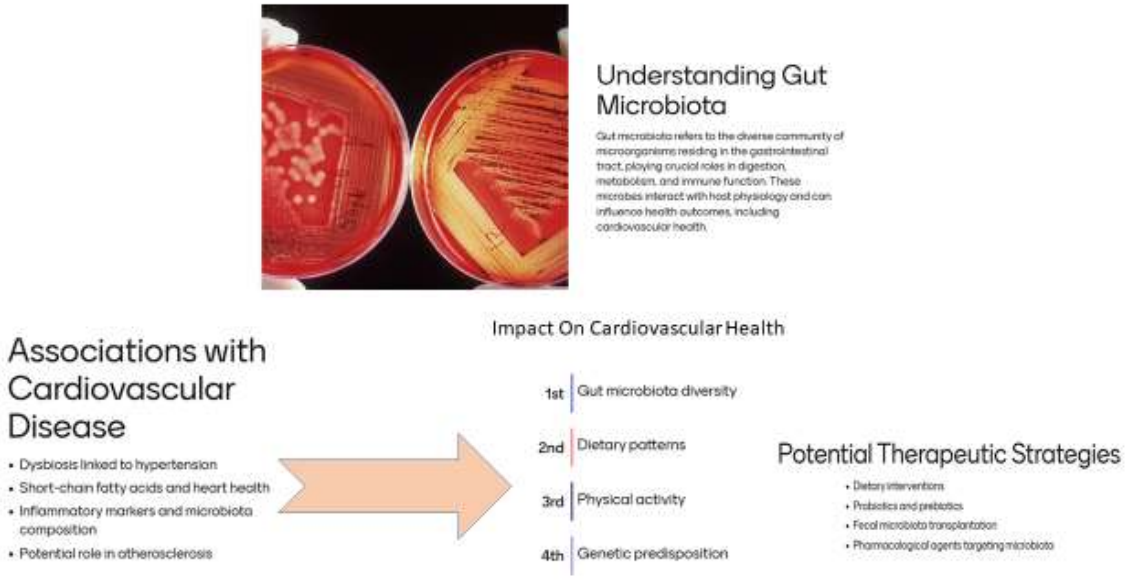


Figure2: Microbiota, Metabolites, and Cardiovascular Diseases -Exploring the Intricate Interactions

Conclusion

Over the past few years, the direct link between gut microbiota and CVDs attracts scientists. Dysbiosis of gut microbiota is related to the progression of atherosclerosis, heart failure, myocardial infarction, hypertension and so on. The metabolites generated from gut microbiota provide insight into how gut microbiota aggravates heart diseases. These findings provide an excellent opportunity to develop interventions targeting the gut microbiota for the treatment of heart diseases. The newer technologies are developed to assess the microbes which produce different metabolites and also to investigate their connection with cardiac diseases which will provide an exciting opportunity in promoting or improving cardiovascular health. Further research is required to illuminate the functions and intrinsic mechanisms of prebiotics and probiotics to consider them as a novel therapeutic approach to cardiovascular disease.

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