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Gut microbiome and cardiovascular disease

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Abstract

Purpose of the review—This review aims to highlight the association between gut microbiome and cardiovascular disease (CVD) with emphasis on the possible molecular mechanisms by which how gut microbiome contributes to CVD.

Recent findings—Increasingly, the roles of gut microbiome in cardiovascular health and disease have gained much attention. Most of the investigations focus on how the gut dysbiosis contributes to CVD risk factors and which gut microbial derived metabolites mediate such effects.

Summary—In this review, we discuss the molecular mechanisms of gut microbiome contributing to CVD, which include gut microbes translocalization to aortic artery due to gut barrier defect to initiate inflammation and microbial derived metabolites inducing inflammation signaling pathway and renal insufficiency. Specifically, we categorize beneficial and deleterious microbial derived metabolites in cardiovascular health. We also summarize recent findings in the gut microbiome modulation of drug efficacy in treatment of CVD and the microbiome mechanisms by which how physical exercise ameliorates cardiovascular health. Gut microbiome has become an essential component of cardiovascular research and a crucial consideration factor in cardiovascular health and disease.

Keywords

Cardiovascular disease (CVD); gut microbiome; microbial metabolites; drug efficacy; physical exercise

INTRODUCTION

Taxonomically well-structured and fine-functional human gut microbiome is essential to human health, such as helping digestion of dietary polysaccharides that enzymes of the host cannot breakdown [1], inducing and training the host immune system [2], producing vitamins (B, K) [3*,4] and maintaining intestinal barrier [5] as well. In healthy humans, commensal and potentially pathogenic bacteria are in a homeostatic balance [6]. Gut microbiome dysbiosis, the condition of dysregulated and disrupted intestinal bacterial

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Conflict of interest

Z.W. is named as co-inventor on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics and therapeutics, and have the right to receive royalty payment for inventions or discoveries related to cardiovascular diagnostics or therapeutics from Cleveland Heart Lab or Procter & Gamble. Y.Z. declares no conflict of interest.

homeostasis, is associated with an array of complex diseases such as inflammatory bowel disease (IBD), obesity, type 1 and type 2 diabetes, cardiovascular disease (CVD), autism, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, rheumatic disease and certain gastrointestinal cancers [6-8, 9*, 10*, 11, 12*]. Remarkably, roles of gut microbiome in CVD have gained much attention, given that CVD are the leading cause of mortality and morbidity. Differences in gut microbiota community between patients with CVD and healthy controls have been investigated in several groups worldwide and Table 1. lists some gut microbiota community shifts with different CVD phenotypes.

Supplementing to those insightful reviews on gut microbiome in CVD [20**, 21**, 22, 23**, 24, 25], here we focus on mechanisms by which and how gut microbiome shapes cardiovascular health and disease, underscoring gut microbiota derived metabolites, the modulatory effect of gut microbiome to cardiovascular drug efficacy and toxicity, the beneficial role of physical exercises in cardiovascular health via modulating the taxonomic composition and function of the human gut microbiome. Uncovering gut microbiome-CVD mechanisms and translating such knowledge into clinical practice are anticipated as primary priority in CVD research. Individual human gut microbiome, drug targets alongside companion and complementary diagnostics, are keys to precision medicine.

Gut barrier defect provides a pathway for gut microbes to inhabit the aortic artery

Gut barrier, comprised of several layers, including the physical barrier composed of gut microbiota, mucus, epithelial cells and the innate and adaptive immune cells [26], plays an important role in health and disease. Gut barrier can prevent bacterium entering circulatory system and the defects have been shown to be associated with gastrointestinal disease (e.g. celiac disease (CeD), inflammatory bowel disease (IBD), colon carcinoma), chronic liver disease, type 1 diabetes, obesity and food allergies [27,28]. Bacterium can be detected in human atherosclerotic plaque of the patients with periodontal disease [29]. However, some bacterium species in atherosclerotic plaque cannot be found in mouth, but can be found in feces, suggesting that gut microbes can also contribute to the atherosclerotic plaque microbial diversity [30]. Gut bacteria enter circulatory system due to gut barrier defect, leading to increased intestinal permeability thereby favoring translocation of gut microbes [31].

A study on 28 patients undergone the carotid endarterectomy by 16S rRNA gene sequencing confirmed that the most abundant bacterium is Proteobacteria alongside three other main phyla, Actinobacteria, Bacteroidetes and Firmicutes found in aortic plaque [32], indicating a large difference from the gut and could be due to environmental discrimination between gut and blood. Bacterium infection can directly drive atherosclerosis. Using B6 *Apoe*^{shl} mouse model with oral infection of *H. cinaedi*, the investigators found that *H. cinaedi* can induce advanced atherosclerotic lesion development by altered expression of cholesterol receptors or transporters and by increased proinflammatory cytokines' expression. These molecular events result in macrophage and neutrophil accumulation, leading to foam cell formation in atherosclerotic lesions [33].

The gut barrier dysfunction and the subsequent increase of intestinal permeability facilitates the translocation of lipopolysaccharide (LPS), also called as endotoxin, from gut lumen to

circulatory blood system. LPS is the outer membrane component of Gram negative bacterium, which protects bacterium from the entry of many noxious compounds [34, 35]. Gram-negative bacteria produce outer membrane vesicles (OMVs) that contain LPS [36]. LPS binds TLR4 to activate NF-κB signaling, leading to overproduction of proinflammatory cytokines and adhesion molecules, therefore resulting in sepsis and atherosclerosis [31, 37]. Besides LPS/TLR4/NF-κB signaling pathway, LPS can also be internalized to cytosol through endocytosis and released into the cytosol, which activates caspase-11, leading to further activation of the NLRP3 inflammasome [38]. The activation of NLRP3 inflammasome leads to caspase-1 activation and IL-1β and IL-18 secretion, which is a key step in the inflammatory process of atherosclerosis [39, 40].

On the other hand, CVD can also induce gut barrier defect, which further exaggerates CVD. Thus, a vicious pathophysiology loop can emerge. An aortic dissection happened in the aorta is characterized by a tear in the inner layer of artery wall, allowing blood to enter into the wall, creating a new passage for blood, known as the “false lumen” [41]. Aortic dissection induces intestinal ischemia and intestinal epithelial barrier dysfunction, thereby leading to the translocation of gut bacteria to the bowel wall and bloodstream, further leading to septic shock [42].

Dietary fiber shows benefit to human health after fermentation by gut microbiota, e.g., the product butyric acid with a function of improving gut barrier [43–45]. Consistently, mice deprived of dietary fiber showed greater epithelial access and lethal colitis [46]. Some nutraceuticals, such as resveratrol, berberine, have been used for clinical trial to treat CVD [47], as preclinical models had shown that these nutraceuticals can improve gut barrier both in vitro cell culture and in vivo animal models[48–50]. Meanwhile, some probiotics, such as *Akkermansia muciniphila*, can improve gut barrier by modulation of mucus layer thickness [51, 52*], which is consistent to its protective effect against atherosclerosis [53].

Gut microbiota derived metabolites and cardiovascular health and disease

In health individuals, gut barrier defects happen only occasionally. Thus, in most cases, gut microbiota leading to CVD is mediated by metabolites. Over the past decades a lot of gut microbial metabolites have received increasing attention. We summarized gut microbiota derived metabolites, related bacteria, target cells of the host, CVD type, putative molecular mechanisms and reference as shown in Table 2.

Some beneficial gut microbial derived metabolites

Gut microbiota can degrade some macromolecules in diet to improve cardiovascular health. As mentioned above, the dietary fiber degraded can produce butyric acid, which can maintain gut barrier and inhibit cholesterol absorption and prevent atherosclerosis [54,55].

Esculin, the glucoside of esculetin, can be hydrolyzed by gut microbes to release free esculetin [56]. Esculetin can significantly inhibit hydrogen peroxide- and Ang-II-induced cell death in human aortic endothelial cells by enhancing NO production via AMPK-mediated eNOS phosphorylation [57].

Anthocyannin has a potential effect as an antiplatelet agent that subsequently can prevent thrombosis and CVD [58]. An earlier study suggests that protocatechuic acid, one gut microbiota metabolite of anthocyanin, decreases miR-10b expression in macrophage, therefore increases ABCA1 and ABCG1 expression and enhances cholesterol reverse transport, leading to attenuation of atherosclerosis [59]. Anthocyannin is a polyphenol compound, which acts as anti-oxidant and can arrest free radicals in human body [60, 61].

Besides anthocyanin, another natural polyphenol, ellagitannin abundant in some fruits, nuts, tea and seeds such as pomegranates, berries and walnuts, shows some cardiovascular benefit [62–65]. However, ellagitannin has a very low bioavailability, and most of the intake ellagitanin from diet cannot reach circulatory system and gut microbes can metabolize ellagitanin as urolithin A or B, which can be absorbed into circulatory system [64,66]. The gut bacteria which can produce urolithin were isolated from human fecal samples, including *Gordonibacter urolithinfaciens* sp. nov. and *Bifidobacterium pseudocatenulatum* INIA P815 [65, 67]. Urolithin A can inhibit endothelial cell migration and decrease the expression of chemokine (C-C motif) ligand 2 and interleukin-8, therefore ameliorate TNFα-induced inflammation and associated molecular markers in human aortic endothelial cells [68], urolithin B-glucuronide can activate eNOS expression, which is considered as an effective strategy for CVD prevention [69].

Enterolactone, a gut microbiota derived metabolite of phytolignans, is a polyphenol compound acting as anti-oxidant, and the low serum concentration of enterolactone is associated with enhanced in vivo lipid peroxidation and increased coronary heart disease- and CVD-related mortality [70, 71].

In addition, gut microbiome modulates host bile acid profile by deconjugation, dehydroxylation and epimerization [72–74], which further affect absorption of cholesterol and triglyceride in small intestine leading to decreased blood cholesterol and LDL [73]. Bile acid receptors, FXR and TGR5, mediate bile acids' effect in increasing reverse cholesterol efflux and further decreasing foam cell formation and atherosclerosis [75–77]. The deconjugation of bile acids in intestine is catalyzed by bile salt hydrolase (BSH) in microbes and the probiotic bacterium expressing BSH shows potential to treat and prevent atherosclerosis [78, 79].

On the other hand, some gut microbial derived metabolites are mechanistically linked to CVD, including trimethylamine N-oxide (TMAO), aromatic amino acid metabolites, p-cresyl sulfate and indoxylsulfate.

TMAO

TMAO is the gut microbiota derived metabolite of phosphatidylcholine, choline, carnitine, γ-buytrobetaine, betaine, trimethyllysine, valerobetaine and ergothioneine as well [80-83, 84*, 85, 86*, 87*, 88]. There are two steps for the biosynthesis of TMAO: the first step is cleavage of precursors with structural moiety containing trimethylamine (TMA) group to form TMA, which is catalyzed by enzymes in gut microbes; the second step is the oxidation of TMA to TMAO by hepatic flavin monooxygenase. The two steps constitute a metaorganismal pathway of TMAO biosynthesis [24]. Several bacterium enzymes involved

in the first step were identified, such as choline TMA lyase (CutC/D), carnitine Rieske-type oxygenase/reductase (CntAB), YeaW/X, betaine reductase and ergothionase [83, 89–92]. In human gut, TMAO reductase is widely distributed in bacterium and can reduce TMAO as TMA [93]. C57BL/6J ApoE$^{-/-}$ mouse is an atherosclerosis-prone mouse model, which develops atherosclerosis similar to humans. The mice fed TMAO supplemented chow diet shows enhanced atherosclerotic plaque when compared with control chow diet, and choline supplemented chow diet enhanced atherosclerosis which is dependent on gut microbiota, whereas the deprivation of gut microbiota by oral supplementation of broad spectrum of antibiotics can attenuate choline promoting atherosclerosis [80]. The fecal microbiota transplant mice model confirmed that microbes from mice tending to develop atherosclerosis can make germ free mice recipient develop larger atherosclerotic plaque compared with atherosclerosis-resistant mice [94]. The other precursors, such as carnitine, γ-butyrobetaine, also show enhanced atherosclerosis which is mediated by gut microbial production of TMAO [82, 83]. Besides atherosclerosis, TMAO can also promote thrombosis [95].

TMAO is mechanistically linked to atherosclerotic CVD and thrombosis through multiple mechanisms. First TMAO enhances endogenous macrophage expression of scavenger receptors, CD36 and SR-A1, leading to uptake of modified LDL to develop foam cells [80]. Second TMAO inhibits expression of the two key bile acid synthetic enzymes, Cyp7a1 and Cyp27a1, and multiple bile acid transporters (Oatp1, Oatp4, Mrp2, and Ntcp) in the liver, therefore decreasing bile acid pool size and subsequent cholesterol excretion [82]. Third TMAO can activate MAPK, NFκB and ROS-TXNIP-NLRP3 inflammasome signaling and promotes recruitment of activated leukocytes to endothelial cells [96, 97]. TMAO also elicits intracellular Ca^{2+} release and activates platelet aggregation, therefore causing thrombosis [95].

Targeting gut microbial metaorganismal pathway of TMAO biosynthesis either by administration of choline TMA lyase inhibitor or by peritoneal injection of anti-sense flavin monooxgenase 3 oligonucleotides shows attenuation of atherosclerosis and thrombosis [98, 99*, 100]. Some methanogenic archaea can consume trimethylamine [101], and the colonization with methanogenic archaea lowers circulating TMAO, indicating a promising way to attenuate atherosclerosis [102*].

In humans, higher levels of circulatory TMAO can track future risk for major adverse cardiac events [81]. Patients with stable heart failure (HF) have significantly higher plasma levels of TMAO than human subjects without HF and TMAO concentrations show significant positive correlation to B-type natriuretic peptide levels [103, 104]. The causality of TMAO and HF has been confirmed by surgical transverse aortic constriction and coronary ligation animal models, which indicates that TMAO increased HF susceptibility and reducing circulating TMAO ameliorates the development of chronic HF [105*]. The association between TMAO and CVD prevalence and cardiac event has been confirmed by other different groups worldwide [106, 107*, 108, 109*, 110*]

TMAO was initially reported as a chemical chaperone and it can stabilize protein conformation by acting as a surfactant for the heterogeneous surfaces of folded proteins [111, 112] TMAO is abundant in marine fish, which acts as cryo-protectant. TMAO

demethylase (TMAOase) in the muscle can catalyze the degradation of TMAO and one product is formaldehyde during fish storage, which constitutes another reason of fish spoilage [113].

Indoxyl sulfate

Indoxyl sulfate is a gut microbial derived metabolite of tryptophan [114, 115]. The metaorganismal biosynthesis of indoxyl sulfate includes microbial cleavage of tryptophan to indole and further oxidized to indoxyl and eventually conjugated as indoxyl sulfate in liver, indoxyl and indoxyl sulfate, which can be excreted to urine [116]. The microbial enzyme, tryptophanase, responsible for cleavage of tryptophan to indole, has been found in *Lactobacillus*, *Bifidobacterium longum*, *Bacteroides fragilis*, *Parabacteroides distasonis*, *Clostridium bartlettii* and *E. hallii* [117].

Plasma indoxyl sulfate was associated with first heart failure event in patients on hemodialysis and predicts major adverse cardiac events in patients with chronic kidney disease [118, 119*]. Indoxyl sulfate is mechanistically linked to CVD through multiple mechanisms. Indoxyl sulfate can induce human umbilical vein endothelial cells (HUVEC) oxidative stress, causing endothelial dysfunction including inhibition of proliferation and nitric oxide production and the anti-oxidant pre-treatment can ameliorate the inhibitory effect [120]. Indoxyl sulfate can also stimulate monocyte to release TNFα through the aryl hydrocarbon receptor (AhR), which further stimulates human vascular endothelial cells to produce CX3CL1, recruiting CD4(+)CD28(−)T cells, which exhibits cytotoxic capability and induces apoptosis in HUVECs, leading to vascular endothelial cell damage [121]. Indoxyl sulfate is also regarded as pro-thrombotic agent. It enhances platelet activities, including causing elevated response to collagen and thrombin and increasing platelet-derived microparticles and platelet-monocyte aggregates [122]. In addition, indoxyl sulfate impairs oxygen sensing in erythropoietin (EPO)-producing cells, thereby suppressing EPO production and resulting in anemia [123, 124].

P-cresyl sulfate

P-cresyl sulfate (PCS) is significantly higher in patients with HF and predicts future risk for a composite event of death or HF-related re-hospitalization [125]. PCS is a gut microbiota derived metabolite of tyrosine, which was processed by at least 4 different enzymes with 4 steps: the first step to the third step are carried out in gut microbes to form intermediates, 4-hydroxyphenylpyruvate, 4-hydroxyphenylacetate and p-cresol; and the last step is to form PCS in gut mucosa or liver [126]. PCS predicts cardiovascular event and all-cause mortality in elderly hemodialysis patients [127]. PCS induces NADPH oxidase activity and reactive oxygen species production contributing to direct cytotoxicity to cardiomyocytes, facilitating cardiac apoptosis and resulting in diastolic dysfunction [128], which is similar to indoxyl sulfate.

Phenylacetylglutamine

Phenylacetylglutamine (PAG) is excreted as a nitrogen waste, which can replace urea in patients lacking carbamyl phosphate synthetase [129]. PAG is a major nitrogenous metabolite that accumulates in uremia [130]. It is a gut microbiota and host co-metabolite of

phenylalanine. Aminotransferase and pyruvate: ferredoxin oxidoreductase A (PorA) in bacterium were involved in the conversion from phenylalanine to phenylacetic acid and the activation of phenylacetic acid to form phenylacetyl-CoA and ligate to glutamine are carried out in human liver and kidney [131, 132]. *Clostridium sporogenes* expresses aminotransferase and PorA [130]. In patients with chronic kidney disease, high serum PAG level is associated with overall mortality and CVD [133].

More gut microbiota derived metabolites were summarized in reference [134], but whether they are involved in CVD pathogenesis or show beneficial effects on cardiovascular health need further investigation.

Gut microbiota derived metabolites contributing to CVD is related to renal insufficiency

TMAO, indoxylsulfate, PCS and PAG are uremic toxins. The elevated levels in circulatory blood is not only dependent on gut microbiome, diet, but also related to renal insufficiency. In non-chronic kidney disease patients, the kidney can excrete those uremic toxins in time without accumulation through tubular secretion [135]. For TMAO, if the fractional renal excretion (%) calculated is based on creatinine, c-mannosyltryptophan, pseudouridine or symmetric dimethylarginine as a surrogate for renal function, it can be higher than 100% [136*], which suggests that TMAO can be easily cleared off. However, in animal models, elevated dietary choline or TMAO directly led to progressive renal tubulointerstitial fibrosis and dysfunction by activating fibrotic TGF-β/Smad3 signaling pathway [137]. So TMAO exacerbates chronic kidney disease progression, which further impairs renal clearance of TMAO. Indoxylsulfate and PCS are protein bound uremic toxins, which are non-dialyzable [138*, 139**]. The kidney plays an important role in mediating the effect of gut microbiota derived metabolites on CVD progression.

Gut microbiome modulates the efficacy of drugs in the treatment of CVD

Gut microbiome can modulate drug efficacy and toxicity and inhibit its metabolism via direct biochemical reactions, such as acetylation, deacylation, decarboxylation, dehydroxylation, demethylation, dehalogenation, deconjugation and β-glucuronidation and indirect pathways through competition for host transporters and enzymes, modulation of host receptor signaling, altering host gene expression and gastrointestinal tract environment [140, 141*].

Statin is a widely used drug to decrease LDL cholesterol. Some patients after statin medication show decreased LDL cholesterol and other patients show no effect [142]. By comparison of gut microbiota from 202 hyperlipidemic patients with statin sensitive (SS) response and statin resistant (SR) response in East China, the investigators found that the SS group shows increased proportion of genera *Lactobacillus*, *Eubacterium*, *Faecalibacterium*, and *Bifidobacterium* and decreased proportion of genus *Clostridium* compared to Group SR group [143*], which suggests gut microbiota community may affect the statin efficacy. The bacterium community enriched in SS group contributing to statin sensitiveness may be related to elevated BSH, which hydrolyzes conjugated bile acid and the free bile acid will not be absorbed to circulatory blood leading to more cholesterol metabolism to bile acid [72, 144].

Monacolin K is a natural statin in some food, such as oyster mushrooms, red yeast rice, and Puerh tea [145], but it has no bioactivity until metabolized to beta-hydroxy acid form (MKA) under alkaline pH. Gut microbiome can catabolize MKA to lose bioactivity [146*].

Digoxin, a drug used for the treatment of atrial fibrillation, atrial flutter, and heart failure, can be inactivated by *Eggerthella lenta* by metabolism to dihydrodigoxin within gastrointestinal tract [147]. A cytochrome-encoding operon, termed the cardiac glycoside reductase, can be activated by digoxin and inhibited by arginine in some *E lenta* strains [148].

On the other hand, drug can also modulate gut microbiome community and affects the gut microbial derived metabolite production. Metformin is a widely prescribed drug to treat multiple diseases such as diabetes, cancer, CVD, Alzheimer's disease, obesity and non-alcoholic fatty liver disease [149]. Metformin reduces cholesterol synthesis in macrophage and increase cholesterol efflux by up-regulating FGF21 expression [150, 151]. A study using 18 healthy individuals taking metformin showed that gut microbiome shift in one day with reduction of inner diversity of gut microbiota and an increase in relative abundance of common gut opportunistic pathogen *Escherichia-Shigella* spp, which are related to the severity of gastrointestinal side effect [152*]. Atorvastatin and rosuvastatin were investigated in an aged mouse model of high-fat diet-induced obesity and fecal microbiota transplantation with fecal material collected from rosuvastatin-treated mouse groups showed improved hyperglycemia [153*]. Aspirin, a drug widely used for antipyretic, analgesic, anti-inflammation and anti-coagulation, also shows gut bacteria discrimination from no medication in four bacteria taxa, *Prevotella spp*, *Bacteroides spp*, family Ruminococcaceae, and *Barnesiella spp* [154].

Physical exercise modulates gut microbiome community beneficial to cardiovascular health

Physical exercise can improve our health and reduce CVD risk by increasing circulatory high density lipoprotein and endothelial nitric oxide production and attenuation of oxidative damage as well [155*]. Intriguingly, physical exercise can also modulate gut microbiome community, showing beneficial effect to cardiovascular health. Physical exercise can increase microbiome richness and Bacteriodetes/Firmicutes ratio, which leads to increased short chain fatty acids production and release of glucogen-like peptide therefore improving insulin sensitivity and decreased lipopolysaccharide (LPS) production as well [156*]. The gut microbiota from exercise mice transplanted to germ free mice shows some benefit to attenuate response to chemical colitis by dextran sodium sulfate compared to sedentary mice [157].

LPS can cause vascular inflammatory responses including lipid accumulation, induced expression of interleukin (IL)-6, IL-8, monocyte chemoattractant protein 1, endothelial cell adhesion molecules, intercellular adhesion molecular-1 and vascular cell adhesion molecule-1 in human coronary artery endothelial cells (HCAECs) via TLR4-NF-κB pathway [158, 159]. LPS is a component of Gram negative bacterium outer membrane and its accumulation due to gut barrier dysfunction induces series inflammatory reaction leading

to sepsis [160, 161]. Exercise can improve gut microbiota profiles, enhance the number of beneficial microbial species and reduce endotoxemia [162*, 163].

Exercise can increase *Clostridiales*, *Roseburia*, *Lachnospiraceae*, *Erysipelotrichaceae*, *Ruminococcaceae* and *Eubacteriaceae* abundance and those taxa are butyrate producers [164*, 165]. Butyrate can lower artery blood pressure by suppressing the prorenin receptor-mediated intrarenal renin-angiotensin system and is inversely correlated with inflammatory markers and serum endotoxin [166*, 167]. In addition, butyrate can maintain gut barrier to prevent endotoxin entering circulatory blood system [168*, 169*].

CONCLUSIONS

Gut microbiome, as an endocrine organ, affects multi-organ health. Gut microbiome can produce short chain fatty acids, modulating immune-response, improving insulin sensitivity and decreasing LPS level, which maintains human organism under a good condition. On the other hand, dysbiosis and unhealthy diet intake lead to gut barrier dysfunction, LPS and uremic toxin accumulation, which speeds up aortic endothelial cell inflammation, atherosclerosis and thrombosis. Some other gut microbiota derived metabolites, TMAO, indoxyl sulfate and p-cresyl sulfate, show clinical relevance of CVD and are mechanistically linked to atherosclerosis, thrombosis and heart failure. Physical exercise can modulate gut microbiome diversity, increase butyrate bacterium producer taxa abundance and attenuate oxidative damage, therefore improving cardiovascular health.

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KEY POINTS

- Increasing evidence has shown that dysbiosis contributes to CVD.
- Gut microbes translocation to aortic artery directly initiates inflammation.
- Gut microbiota derived metabolites mediate the effects of gut microbiome contributing to cardiovascular health and disease.
- Gut microbiome modulates the drug efficacy in the treatment of CVD.
- Physical exercise can modulate gut microbiome to ameliorate cardiovascular health.

Table 1.

Gut microbiome and cardiovascular disease.

Cardiovascular disease phenotype	Microbiota community shift	References
hypertension	*Prevotella* and *Klebsiella*↑	[13]
heart failure	*Faecalibacterium prausnitzii*↓ *Ruminococcus gnavus*↑	[14]
coronary artery disease	Lactobacillales, *Escherichia-Shigella* and *Enterococcus*↑ *Faecalibacterium*, *Subdoligranulum*, *Roseburia* and *Eubacterium rectale*, Bacteroidetes↓	[15,16]
ischemic stroke	*Atopobium cluster* and *Lactobacillus ruminis*↑ *Lactobacillus sakei*↓	[17]
atrial fibrillation	*Ruminococcus*, *Streptococcus* and *Enterococcus*↑ *Faecalibacterium*, *Alistipes*, *Oscillibacter* and *Bilophila*↓	[18]
atherosclerotic cardiovascular disease	*Enterobacteriaceae.Escherichia coli, Klebsiella spp., Enterobacter aerogenes, Streptococcus spp.,Lactobacillus salivarius, Solobacterium moorei, Atopobium parvulum, Ruminococcus gnavus*, and *Eggerthella lenta* ↑ *Roseburia intestinalis, Faecalibacterium cf. prausnitzii, Bacteroides spp., Prevotella copri,* and*Alistipes shahii*↓	[19]

Table 2.

Gut microbiota derived metabolites and cardiovascular health and disease

Metabolite	Substrate	Gene/enzyme	Bacteria	Biological Effects	Host target	Disease	Ref.
esculetin	esculin	NA	*Enterococcus faecalis*, *Selenomonas ruminantium* 2358, et al.	↑NO	aortic endothelial cell	atherosclerosis	56-57
protocatechuic acid	anthocyanin	NA	NA	↓miR-10b, ↑ABCA1 and ABCG1	macrophage	atherosclerosis	58-61
urolithin	ellagitannin	NA	*Gordonibacter urolithinfaciens* sp. nov. and *Bifidobacterium seudocatenulatum* INIA P815	Inhibiting endothelial cell migration, ↓ chemokine ligand 2 and IL-8, ↑ eNOS	endothelial cell	atherosclerosis	62-69
enterolactone	phytolignan	NA	NA	↓lipid peroxidation	NA	heart disease- and CVD-related mortality	70-71
TMAO	phosphatidylcho-line, choline, carnitine, buytrobetaine, betaine, trimethyllysine, valerobetaine, ergothioneine	cutC/D, yeaW/X, Grdh, egtA, egtB, egtC, egtD, egtE, torA	Diverse	↑CD36, SR-A1 ↓Cyp7a1 and Cyp27a1, ↑MAPK, NFκB, NLRP3 signaling ↑Ca^{2+} release	macrophage, endothelial cell, platelet	atherosclerosis, thrombosis	80-110
indoxyl sulfate	tryptophan	NA	*Lactobacillus*, *Bifidobacterium longum*, *Bacteroides fragilis*, *Parabacteroides distasonis*, *Clostridium bartlettii* and *Eubacterium hallii*	↑oxidative stress, ↓nitric oxide, ↑TNFα	monocyte, vascular endothelial cells	adverse cardiac event	114-124
p-cresyl sulfate	tyrosine	Tyrosine phenol-lyase (EC 4.1.99.2.),tyrosine transaminase (EC 2.6.1.5.) or by aromatic-amino-acid transaminase (EC 2.6.1.57.), phenylalanine dehydrogenase (EC 1.4.1.20.),p-hydroxyphenylpyruvate oxidase,p-hydroxyphenylacetate decarboxylase	Bacteroidaceae, Bifidobacteriaceae, Clostridiaceae, Enterobacteriaceae, Enterococcaceae, Eubacteriaceae, Fusobacteriaceae, Lachnospiraceae, Lactobacillaceae, Porphyromonadaceae, Staphylococcaceae, Ruminococcaceae, Veillonellaceae	↑ NADPH oxidase, ↑ROS,	cardiomyocyte	cardiovascular event and all-cause mortality in elderly hemodialysis patients	126-128
phenylacetylglutamine	phenylalanine	amino transferase (Aat), PorA,	*Clostridium sporogenes*,	NA	NA	Cardiac event	133

NA, not available; CVD, cardiovascular disease. ↑ ↓ increases or decreases compared with control, respectively.