Review

Gut Microbiota and Their Metabolites as Modulators of Vascular Complications in Diabetes

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Abstract: With the global rise in population and aging, along with the increasing burden of overweight and obesity, the prevalence of diabetes is expected to surge dramatically. Microvascular and macrovascular complications are the leading causes of death among patients with type 2 diabetes. Recent advancements have provided evidence suggesting that gut microbiota directly or indirectly regulate vascular function. This review focuses on the complex interactions between gut microbiota and its metabolites and vascular complications of diabetes. In particular, we highlight the novel therapeutic effects of interventions such as probiotics, dietary modifications, and fecal microbiota transplantation in improving gut microbiota composition and reducing the risk of vascular complications in diabetes. These findings not only provide new insights into the pathological mechanisms of diabetic vascular complications but also reveal ideas for guiding the formulation of future treatment strategies.

Keywords: gut microbiota; metabolites; vascular complications; diabetes

1. Introduction

Diabetes mellitus (DM) is a major global health concern that significantly contributes to the development of various complications, particularly diabetic vascular disease [1]. The increasing prevalence of stroke, coronary heart disease (CHD), acute myocardial infarction (AMI), diabetic retinopathy (DR), and diabetic nephropathy (DN) in diabetic patients underscores the urgent need for more effective therapeutic strategies [1]. However, conventional treatments, including blood glucose regulation and anti-inflammatory therapies, remain insufficient in preventing or reversing the progression of diabetic vascular complications.

Emerging evidence suggests that the gut microbiota and its metabolites play a pivotal role in the pathogenesis of diabetes and its vascular complications. The gut microbiota, through its complex interactions with the host's immune and metabolic systems, influences the development of inflammation, endothelial dysfunction, and metabolic disturbances that underlie diabetic vascular complications [2]. Metabolites produced by gut microbiota, such as short-chain fatty acids (SCFAs) and bile acids [3], have been shown to modulate systemic inflammation, insulin sensitivity, and vascular health, making them potential therapeutic targets [4,5].

Despite these promising insights, current clinical approaches largely overlook the influence of gut microbiota in diabetes management, and treatment options for diabetic vascular complications remain limited. This gap in understanding and treatment presents an opportunity for microbiota-based therapies, such as probiotics, prebiotics, and dietary interventions, to be explored as novel strategies to prevent or mitigate the progression of these complications. Targeting gut microbiota composition and its metabolites may promote the implementation of personalized and effective treatment options for diabetic patients with vascular disease, ultimately improving clinical outcomes.

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2. Overview of Gut Microbiota and Their Metabolites in Diabetes

Gut microbiota play a significant role in the onset and progression of diabetes. Recent studies have shown that the gut microbiota composition and its metabolites (e.g.; SCFAs, TMAO) contribute to the metabolic dysregulation observed in diabetes. First, dysbiosis of gut microbiota has been linked to insulin resistance in diabetes. Research has demonstrated that gut bacteria influence gut barrier function and immune responses, which lead to increased systemic inflammation and impaired insulin sensitivity. Additionally, gut-derived metabolites like SCFAs have been shown to modulate immune cells, enhance gut barrier integrity, and reduce systemic inflammation, which may positively influence glucose metabolism. On the other hand, metabolites such as TMAO exacerbate vascular dysfunction and oxidative stress, which may contribute to the progression of diabetes-related complications. In the following sections, we delve into how gut microbiota and their metabolites contribute to the development of diabetic cardiovascular disease, nephropathy, retinopathy, and other complications.

3. Gut Microbiome Associated with Macrovascular and Microvascular Complications in Diabetes

Hyperglycemia, lipid accumulation, and oxidative stress are common causes of vascular complications in diabetes, resulting in endothelial dysfunction, platelet dysfunction, and coagulation abnormalities. These pathophysiological changes contribute to both macrovascular and microvascular complications. Recent research has highlighted the role of gut microbiota in these processes. Over the past two decades, studies have revealed significant differences in gut microbiota composition and metabolites between healthy individuals and those with macrovascular and microvascular complications of diabetes, suggesting that dysbiosis may play a role in the development and progression of these complications (Table 1).

3.1. Ischemic Stroke

Recently, the functional relationship between the gut microbiota and brain function, known as the "gut-brain axis," has emerged as a novel field in neuroscience [6]. This axis is essential in the modulation of the immune response and potentially affects outcomes of neurological conditions, such as stroke. Interestingly, despite this emerging understanding, many large clinical studies have failed to support the use of prophylactic antibiotics to reduce post-stroke mortality. For instance, data from 506 stroke patients showed that prophylactic antibiotics reduced overall infections by 14% [7]. However, the prophylactic use of ceftriaxone did not lead to improved functional outcomes in adults with acute stroke after 3 months [8]. Additionally, one study found that administering prophylactic antibiotics to patients with severe acute ischemic stroke was associated with an increased risk of infections during hospitalization and did not reduce short-term mortality risk, highlighting the limited benefit of this intervention [9].

Animal studies further illustrate the complex relationship between gut microbiota and stroke outcomes. Depleting the gut microbiota of mice with broad-spectrum antibiotics before inducing stroke led to increased post-stroke mortality, independent of infarct size [10]. In another study, Xia et al. transplanted fecal samples from stroke patients into germ-free mice, resulting in severe brain damage in the mice, accompanied by an increase in IL-17^{+} γδ T cells in the gut [11]. These findings suggest that gut microbiota dysbiosis can trigger immune responses and alter host homeostasis, thereby impacting stroke outcomes. This evidence highlights the complex and sometimes counterproductive effects of manipulating gut microbiota with antibiotics in the context of stroke, emphasizing the need for deeper investigations into the gut-brain axis in stroke management.

There is growing evidence that the relationship between stroke and gut microbiota is bidirectional: stroke can lead to gut microbiota dysbiosis, while dysbiosis in the gut microbiota may, in turn, determine stroke prognosis and recovery. Wang et al. conducted a bidirectional Mendelian Randomization analysis using gut microbiota, blood metabolites, and stroke data from the largest genome-wide association studies [12]. The results showed a causal relationship between stroke and the *Bifidobacteriales order*, *Bifidobacteriaceae* family, and *Desulfovibrio* genus. All three taxa were positively correlated with ApoA1 and HDL-PL, while *Desulfovibrio* was negatively correlated with ApoB/ApoA1 [12]. Similarly, Li et al. observed distinct changes in gut microbiota composition based on stroke severity. In mild stroke patients, levels of Enterobacter, *Pyramidobacter*, and the *Erysipelotrichaceae* family increased, while in severe stroke patients, levels of *Ruminococcaceae* and *Christensenellaceae* increased. Furthermore, *norank_O_Mollicutes_RF9*, *Enterobacter*, and *Ruminococcaceae* were negatively correlated with LDL, HDL, and blood glucose levels, while *Christensenellaceae* and *Ruminococcaceae* were positively correlated with NIHSS1M and mRS scores [13].

However, most conclusions drawn from observational and preclinical studies are largely inconsistent. For example, Xia et al. found that core human microbiota members, such as *Prevotella* and *Faecalibacterium*, were reduced in patients with acute ischemic stroke or transient ischemic attack. Fecal transplants from stroke patients

caused severe brain damage in mice [11]. *Escherichia coli* is a typical bacterium of the *Enterobacteriaceae* family. Inoculation of *Escherichia coli* strains isolated from mice treated with MCAO into antibiotic-treated mice resulted in a significant increase in cerebral infarction. However, reducing nitrate production with aminoguanidine or superoxide dismutase, or inhibiting nitrate respiration with tungstate, could prevent *Enterobacteriaceae* overgrowth, reduce systemic inflammation, and decrease cerebral infarction [14]. On the other hand, another case-control study reported an increase in these bacteria in stroke patients [15]. In a monkey model of left middle cerebral artery occlusion, *Prevotella* was increased, while *Faecalibacterium* was reduced [16]. Yet, in a mouse model, both species were found to be deficient three days after middle cerebral artery occlusion [17]. Additionally, there are conflicting reports on the role of *Akkermansia muciniphila* and *Odoribacter* species following stroke. Some studies suggest that stroke-induced changes in microbial composition lead to an overabundance of *Akkermansia muciniphila* and *Odoribacter* species in post-stroke mice [18]. In contrast, other studies observed a reduction in *Akkermansia* in stroke patients [19], while yet another reported a significant increase post-stroke [13].

These conflicting findings highlight the complexity of the gut microbiota's role in stroke and suggest that the roles of bacteria such as *Prevotella, Faecalibacterium*, *Akkermansia*, and *Odoribacter* warrant further investigation. Understanding the causal relationships between gut microbiota and stroke, as well as the underlying mechanisms involved, remains a crucial area for future research.

3.2. Coronary Heart Disease

Coronary heart disease (CHD) is a condition caused by coronary artery lesions and insufficient blood supply to the myocardium, typically stemming from atherosclerosis or thrombosis in the coronary arteries. Acute myocardial infarction (AMI) is one of the severe manifestations of CHD. The gut microbiota and its metabolites play a crucial role in the development and progression of AMI. Compared to healthy controls, AMI patients have higher levels of genera such as *Megasphaera*, *Butyricimonas*, *Acidaminococcus*, and *Desulfovibrio*, while *Tyzzerella 3*, *Dialister*, *Bacteroidales ventriosum* group, *Pseudobutyrivibrio*, and family *ND3007* (*Erysipelotrichaceae*) show reduced abundance [20]. A biomarker study in AMI patients demonstrated that a combination of 14 genera, including *Streptococcus*, *Alistipes*, *Butyricicoccus*, and *Prevotella*, effectively differentiated AMI from stable CAD, with an AUC value of 0.831, indicating the potential utility of monitoring gut microbiota changes to predict disease progression [21]. In a myocardial infarction rat model, recent research revealed that gut microbiota diversity, particularly involving the phyla *Synergistetes* and *Spirochaetes*, as well as families such as *Erysipelotrichaceae*, *Syntrophomonadaceae*, *Lactobacillaceae*, and *Bifidobacteriaceae*, was closely associated with AMI [22]. Most *Erysipelotrichaceae* bacteria are butyrate producers, and studies have demonstrated that sodium butyrate can improve cardiac dysfunction following AMI in rats when directly injected into the ischemic region [23]. Therefore, timely supplementation with butyrate or butyrate-producing strains (such as *Erysipelotrichaceae*) may represent a potential therapeutic strategy for AMI.

Coronary artery disease (CAD) is defined as the accumulation of atherosclerotic plaques in the coronary arteries, leading to arterial stenosis and hardening, which restricts blood flow to the heart. CAD is the primary cause of CHD and is also linked to changes in gut microbiota. Research by Emoto et al. found an increased abundance of *Lactobacillales* in CAD patients, while the phylum Bacteroidetes, including *Bacteroides* and *Prevotella*, was decreased. This finding suggested that an elevated Firmicutes/Bacteroidetes ratio could be a potential marker for CAD [24]. Choroszy et al. conducted a systematic review and meta-analysis, further clarifying the association between CAD and specific gut microbiota changes. They reported that the alpha diversity was significantly reduced in CAD patients, accompanied with a decrease in Bacteroidetes and *Erysipelotrichaceae*, while *Enterobacteriaceae*, *Lactobacillus*, and *Streptococcus* levels were increased [25]. Xue et al. also reported a reduction in beneficial bacteria such as *Prevotella copri*, *Clostridium butyricum*, and *Roseburia intestinalis* in CAD patients, whereas *Fusobacterium varium*, *Rodentibacter rodentium*, and *Eubacterium ventriosum* were enriched [26]. Notably, the study by Xue et al. highlighted that *Clostridium* and *Faecalibacterium* are key microbes involved in the production of indolepropionic acid (IPA) from tryptophan. Metabolic analyses revealed a significant depletion of the tryptophan metabolism pathway in CAD samples, indicating reduced tryptophan metabolism capacity in the gut microbiome of CAD patients [26]. Mechanistic studies showed that IPA enhances macrophage reverse cholesterol transport by inhibiting miR-142-5p expression, thereby reducing atherosclerotic plaque burden [26]. This suggests that IPA supplementation or the restoration of related microbial populations may offer a novel therapeutic strategy for CAD.

Atherosclerosis is the main cause of CHD, leading to obstruction of blood flow in the coronary arteries and inducing myocardial ischemia and related complications, such as angina pectoris and myocardial infarction. In the context of AS, a Swedish study involving 12 AS patients and 13 controls revealed a higher abundance of

Collinsella in AS patients, while *Roseburia* and *Eubacterium* were more prevalent in the control group [27]. Another study involving 218 AS patients found significant differences in gut microbiota composition compared to healthy individuals, specifically with increased levels of *Enterobacteriaceae* (such as *Escherichia coli*, *Klebsiella*, and *Enterobacter*) and *Streptococcus* [28]. Furthermore, recent research demonstrated that two species of the *Bacteroides* genus, *Prevotella copri* and *Bacteroides dorei*, effectively prevented atherosclerosis in a mouse model lacking apolipoprotein E. Oral administration of these bacteria significantly reduced the formation of atherosclerotic lesions, highlighting their protective potential [29].

The majority of previous studies focused on strategies for reducing beneficial bacteria and their impact on CVD, but less attention has been given to the role of impact of harmful bacteria such as *Fusobacterium variabilis*, *Bacillus rodentium*, *Eubacterium ventricularis*, *Enterobacteriaceae*, and *Streptococcus*. Inhibiting the growth of harmful bacteria may be a promising intervention for conditions like AMI, CAD, and AS.

3.3. Diabetic Retinopathy

Orešić et al. were the first to report evidence suggesting that gut microbiota may influence the lipid composition of the eye. Compared to germ-free mice, conventionally raised mice exhibited higher oxidative stress due to the influence of gut microbiota, which led to a decrease in phosphatidylcholine and an increase in plasmalogen ethanolamine in the lens [30]. Wang et al. found that intermittent fasting in diabetic mice with retinal degeneration increased the levels of *Firmicutes* in the gut, while *Bacteroidetes* and *Verrucomicrobia* levels decreased [31]. These findings suggest a potential link between gut microbiota and DR.

In patients with DR, the diversity and abundance of gut microbiota are disrupted. Clinical studies have demonstrated that patients with DR exhibit changes in gut microbiota diversity and abundance. Das et al. found that pro-inflammatory bacteria such as *Streptococcus* were reduced, while amino acid-fermenting bacteria, *Escherichia coli*, and *Enterobacter* were significantly increased compared to healthy individuals [32]. Bai et al. reported higher microbial richness in DR patients, with increased levels of *Bacteroidetes, Proteobacteria*, and *Desulfovibrio*, while *Firmicutes* were decreased [33]. Additionally, *Bacteroides* and *Desulfovibrio* levels were significantly higher in DR patients compared to those with diabetes alone. These Gram-negative bacteria produce LPS, which can induce inflammatory damage, disrupt metabolic homeostasis, and inhibit endotoxin tolerance, potentially contributing to the development of retinopathy [34]. The proliferation of *Escherichia coli* can also increase uric acid levels and produce reactive oxygen species, leading to neuronal apoptosis and severe damage to retinal endothelial cells, thereby promoting DR [35]. A systematic review and meta-analysis revealed that compared to patients with T2DM, DR patients had lower alpha diversity, with a significant increase in the relative abundance of Bacteroidetes and a notable decrease in Firmicutes, Proteobacteria, and Actinobacteria[36].

However, few studies have explored the effects of probiotics on DR in murine models, and relevant human data are unavailable. Future research should focus on conducting clinical trials to evaluate the efficacy of probiotics in DR patients, as well as exploring the mechanisms by which probiotics could modulate gut microbiota to alleviate DR symptoms.

3.4. Diabetic Nephropathy

The concept of the "gut-kidney" axis, first proposed by Meijiers in 2011 [37], suggests a dynamic interaction between the gut microbiota and kidney function. Multiple studies have consistently demonstrated that patients with DN experience significant quantitative and qualitative changes in their gut microbiota, leading to dysbiosis that disrupts the symbiotic relationship between the gut and the host [38]. A prominent feature of this dysbiosis is the reduction of bacteria that produce SCFAs, which are known to have anti-inflammatory and renal protective effects. Supporting this, research has shown that antibiotics that deplete the gut microbiota can alleviate renal tubular interstitial injury and reduce lipid accumulation in diabetic rat models of DN [39]. These findings suggest that changes in gut microbiota may have a causal effect on the development of DN through the gut-kidney axis.

Further clinical studies have reinforced the importance of gut microbiota in DN. For instance, Chen et al. [40] revealed correlations between clinical parameters and gut microbiota in DN patients. The study found that 24-h urinary protein levels were positively correlated with *Alistipes* and *Subdoligranulum*, while cholesterol levels were positively associated with *Bacteroides* and *Lachnoclostridium*. Additionally, a negative correlation was observed between the estimated glomerular filtration rate (eGFR) and the *Ruminococcus* torques group. These findings highlight the potential role of specific gut bacteria in the progression of DN. Likewise, Zhang et al. [41] aimed to identify bacterial biomarkers associated with the progression of DN by studying changes in bacterial composition at different stages of the disease. Their results showed that, compared to diabetic patients without nephropathy, patients in both early and late stages of DN had significantly higher levels of *Fusobacterium*, *Parabacteroides*,

and *Ruminococcus gnavus. Anaerotruncus, Prevotella 9*, and *Roseburia* were positively correlated with eGFR. These bacteria were also negatively correlated with markers of kidney damage such as microalbuminuria, 24-h urinary protein, and serum creatinine. *Anaerotruncus*, in particular, shows promise as a potential biomarker for distinguishing different stages of DN.

However, despite these associations, the exact causal relationship between gut microbiota dysbiosis and DN progression remains to be fully clarified, and further research is needed to determine the mechanisms involved.

In summary, numerous studies have shown significant changes in the composition of the gut microbiota between patients with diabetic vascular complications and healthy individuals. Despite these promising findings, some knowledge gaps remain. First, most findings are derived from observational studies, and the causal relationship remains to be clarified. In addition, there is some heterogeneity in the results, and the changes in the gut microbiota reported by different studies are sometimes inconsistent, such as the differences in the behavior of *Prevotella* and *Faecalibacterium* in various stroke models. The extrapolation between animal models and human data is also limited, and the feasibility of clinical application requires further validation. Future research should focus on verifying the causal relationship between the gut microbiota and vascular complications through longitudinal studies and large-scale clinical trials. Integrating multi-omics approaches and personalized medicine will also help to reveal the complex interactions between the gut microbiota and host metabolism, ultimately providing more effective prevention and treatment strategies for cardiovascular disease.

Table 1. Clinical research on gut microbiota in diabetic vascular complications.

Year	Location	Disease Condition	Participants	Sample Detection	Changes in the Gut Bacteria	Ref.
2017	Denmark	Prediabetes	Prediabetes (134) and normal glucose regulation (134)	16S rRNA sequencing	↑ *Dorea, [Ruminococcus]*, *Sutterella* and *Streptococcus* ↓ *Clostridium*	[42]
2021	China	T2DM with IS	AIS patients (90), HC (55)	16S rRNA sequencing	↑ *Parabacteroides*, *Ruminococcus* ↓ *Prevotella*, *Faecalibacterium*, *Lachnospira*, and *Coprococcus*	[43]
2018	China	T2DM with IS	AIS patients (49), HC (30)	16S rRNA sequencing	↑ *Bacteroides*, *Megamonas* ↓ *Bifidobacterium*, *Roseburia,*	[44]
2021	China	T2DM with IS	AIS patients (28), HC (28)	16S rRNA sequencing	↑ *Enterobacteriaceae, Ruminococcacaceae, and Veillonellaceae* ↓ *Bacteroidaceae, Prevotellaceae*	[14]
2015	China	IS	AIS patients (104), and HC (90)	16S rRNA sequencing	↑ *Parabacteroides, Oscillospira,* and *Enterobacteriaceae* ↓ *Prevotella, Roseburia,* and *Fecalibacterium*	[11]
-	Europe	IS	AIS patients (60,176), HC (1310,725)	16S rRNA sequencing	↑ Lachnoclostridium, Bilophila, and Barnesiella ↓ Lentisphaerae, Lentiephaeria, Victivallales, and Euryarchaeota	[12]
2019	China	IS	AIS patients (30), HC (30)	16S rRNA sequencing	↑ Odoribacter, Akkermansia, Ruminococcaceae, and Victivallis ↓ Anaerostipes, Ruminiclostridium	[13]
2014	China	IS	AIS patients (322), and HC (231)	16S rRNA sequencing	↑ Escherichia/Shigella, Parabacteroides, and Alistipes ↓ Bacteroides, Prevotella, and Faecalibacterium	[15]
2015	China	IS	AIS patients (8), and HC (10)	16S rRNA sequencing	↑ Megamonas, Dialister, Bifidobacterium, and Ruminococcus ↓ Bacteroides, Parabacteroides, Akkermansia, and Prevotella	[19]
2021	China	SCAD with T2DM	SCAD with T2DM (38), HC (55)	Metagenome sequencing	↑ *Bifidobacterium longum, Bifidobacterium catenulatum,* and *Ruminococcus torques* ↓ *Alistipes putredinis* and *Roseburia inulinivorans*	[45]

Table 1. *Cont.*

Year	Location	Disease Condition	Participants	Sample Detection	Changes in the Gut Bacteria	Ref.
2017	Spain	CAD with T2DM	CAD with T2DM (16), CAD withour T2DM (16)	16S rRNA sequencing	↑ *Oscillospira*, *Phascolarctobacterium*, *Streptococcus*, and *Desulfovibrio* ↓ *Bacteroides*, *Prevotella*, *Odoribacter*, and *Roseburia*	[46]
2024	China	CHD	Diabetic coronary heart disease (57), HC (36)	Microbiome sequencing	↑ *Collinsella aerofaciens*, *Bacteroides vulgatus*, *Eubacterium eligens*, and *Bacteroides uniformis* ↓ *Eubacterium hallii*, *Anaerostipes hadrus*, and *Ruthenibacterium lactatiformans*	[47]
2016	China	AMI	AMI patients (49), HC (48)	Metagenome sequencing	↑ Coprococcus catus, Ruminococcus brinii, Ruminococcus torques, and Alistipes putredinis	[21]
2017	China	ASCVD	ACVD patients (218), HC (187)	Metagenome sequencing	↑*Ruminococcus gnavus*, *Eggerthella lenta*, and *Enterobacter aerogenes*, ↓ *Roseburia intestinalis* and *Faecalibacterium* cf. *prausnitzii*	[28]
2014	Japan	CAD	CAD patients (30), and controls without CAD (30)	16S rRNA sequencing	↑*Faecalibacterium prausnitzii* and *Prevotella copri* ↓*Bacteroides vulgatus, and Bacteroides dorei*	[29]
2022	China	DR	DR patients (25), HC (25)	16S rRNA sequencing	↑ *Megamonas*, *Ruminococcus torques* group, and *Lachnoclostridium*, ↓ *Blautia*, *Eubacterium hallii*, *Collinsella*, and *Dorea*	[33]
2021	India	DR	T2DM with DR (28), HC (30)	16S rRNA sequencing	↑ *Dialister*, *Akkermansia*, ↓ *Prevotella*, *Megasphaera*, *Faecalibacterium*	[32]
2021	China	DR	DR (25), HC (25)	16S rRNA sequencing	↑ *Acidaminococcaceae*, and *Tannerellaceae* ↓ *Peptostreptococcaceae*, *Streptococcaceae*, *Eggerthellaceae*, and *Butyrlclcoccaceae*	[48]
2017	China	ESRD	ESRD (52), HC (60)	qPCR	↑ *Bacteroides*, *Escherichia*, *Subdoligranulum*, and *Fusobacterium* ↓ *Prevotella*, *Roseburia*, *Faecalibacterium*, and *Megemonas*	[49]
2018	China	DN	DN patients (43), HC (37)	16S rRNA sequencing	↑ *Megasphaera*, *Veillonella*, *Escherichia Shigella*, and *Anaerostipes*	[38]
2017	China	DN	DN patients (14), and HC (14)	16S rRNA sequencing	↑ *Escherichia Shigella* ↓ *Prevotella_9*	[50]

Abbreviations: AMI, acute myocardial infarction; AS, atherosclerosis; atherosclerotic cardiovascular disease, ASCVD; CAD, coronary artery disease; DR, diabetic retinopathy; DN, diabetic nephropathy; End stage renal disease, ESRD; Healthy controls, HC; Ischemic stroke, IS; stable coronary artery disease combined with diabetes mellitus, SCAD with T2DM.

4. Diet-Derived Microbial Metabolites Modulate Vascular Complications in Diabetes

he interaction between gut microbiota and the host plays a crucial role in regulating vascular health, particularly through diet-derived microbial metabolites produced by fermentation. Metabolites such as SCFAs, BAs, and TMAO, etc have been identified as key regulators of vascular function and are increasingly recognized for their role in the development of vascular complications in diabetes (Figure 1, Table 2).

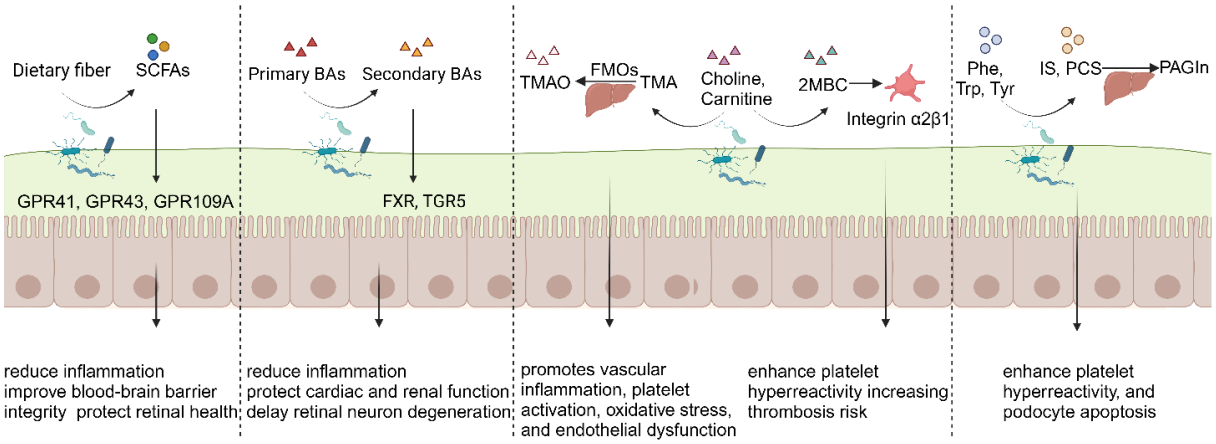

Figure 1. The gut microbiota dysbiosis and its metabolites are involved in the development of diabetic vascular complications (created with BioRender.com).

Dysbiosis of the gut microbiota and its metabolites are implicated in diabetic vascular complications, including stroke, coronary artery disease, retinopathy, and nephropathy. SCFAs produced from a high-fiber diet interact with GPCRs to regulate inflammation, improve blood-brain barrier integrity, reduce vascular and renal inflammation, and protect retinal health. Secondary bile acids, converted by gut bacteria, interact with FXR and TGR5 receptors to reduce inflammation, protect cardiac and renal function, and delay retinal neuron degeneration. TMAO, generated from dietary choline and carnitine, ultimately promotes vascular inflammation, platelet activation, oxidative stress, and endothelial dysfunction, contributing to vascular and renal damage. Additionally, 2MBC enhances platelet hyperreactivity, increasing thrombosis risk. High-protein diets lead to the production of uremic toxins, such as pCS, IS, and PAGln, which increase platelet aggregation and are linked to cardiovascular mortality in renal impairment. Abbreviations: SCFAs, short-chain fatty acids; GPCRs, G protein-coupled receptors; FXR, Farnesoid X receptor; TMAO, Trimethylamine N-oxide; TMA, trimethylamine; FMOs, flavin-containing monooxygenases, Tyr, tyrosine; Trp, tryptophan; Phe, phenylalanine; pCS, p-cresol sulfate; IS, indoxyl sulfate; PAGln, phenylacetylglutamine.

4.1. Short-Chain Fatty Acid

SCFAs are small organic monocarboxylic acids produced by intestinal microbiota through the fermentation of dietary fibers and resistant starches, which are indigestible carbohydrates. The primary SCFAs include acetate, propionate, and butyrate [51], typically in a molar ratio of roughly 60, 20, 20 [52]. The intestine generates approximately 500–600 mmol of SCFAs daily [53]. After their synthesis, SCFAs are absorbed by colonic cells via H+-dependent or sodium-dependent monocarboxylate transporters. Unabsorbed SCFAs enter the portal circulation and are primarily used as energy substrates by the liver.

SCFAs exert various physiological functions by interacting with intestinal epithelial cell G protein-coupled receptors (GPCRs), such as GPR41, GPR43, and GPR109A. Through these receptors, SCFAs regulate insulin secretion, modulate inflammatory responses, and maintain intestinal barrier integrity, all of which are critical for managing the vascular complications associated with diabetes.

4.1.1. SCFAs: Role in Ischemic Stroke

Clinical trials have shown that stroke patients exhibit a reduction in beneficial SCFAs-producing bacteria, including *Blautia*, *Roseburia*, *Anaerostipes*, *Bacteroides*, and *Faecalibacterium* [11,13,54]. This reduction suggests that decreased SCFAs levels may negatively impact brain function, particularly in stroke rehabilitation.

At the brain level, SCFAs can exert direct and indirect effects by modulating the immune and autonomic nervous systems. SCFAs have been shown to cross the blood-brain barrier readily [55,56], and reduced levels of SCFAs have been observed in both stroke patients and animal models, such as those with middle cerebral artery occlusion (MCAO) [54,57]. Following ischemic stroke, microglial activation releases inflammatory molecules and reactive oxygen species [58]. However, SCFAs stimulation has been found to suppress microglial activation and enhance the integrity of the blood-brain barrier [59]. Mechanistic studies suggest that SCFAs may regulate key

proteins involved in blood-brain barrier tight junctions, such as claudin-5, thereby inhibiting microglial activation and preventing increased blood-brain barrier permeability [60,61]. Furthermore, SCFAs may not only modulate resident microglia but also influence lymphocyte function through their peripheral effects [62]. While these findings highlight the potential neuroprotective role of SCFAs, the exact mechanisms remain to be fully elucidated.

In animal studies, interventions targeting gut microbiota have shown promising results in elevating SCFAs levels. For instance, intermittent fasting altered gut microbiota composition in mice with cerebral ischemia, increasing SCFAs levels and improved outcomes [63]. Another study using a combination therapy of tanshinone IIA-loaded nanoparticles and neural stem cells demonstrated that elevating SCFAs levels reduced intestinal inflammation, restored gut homeostasis, and enhanced recovery in a pig model of ischemic stroke [64].

In summary, the complex relationship between gut microbiota, SCFAs, and stroke outcomes underscores the potential for therapeutic interventions targeting gut health to mitigate stroke-related damage. Future research should focus on elucidating the precise mechanisms by which SCFAs influence neuroinflammation and promote brain repair. Such studies may pave the way for novel treatment strategies that harness the gut-brain axis to improve outcomes in stroke patients.

4.1.2. SCFAs: Role in Coronary Heart Disease

One study found that the levels of certain bacterial genera, including *Megasphaera*, *Butyricimonas*, *Acidaminococcus*, and *Desulfovibrio*, were higher in AMI patients compared to healthy controls, while the levels of *Tyzzerella 3*, *Dialister*, *Pseudobutyrivibrio*, and *Lachnospiraceae ND3007* were lower [20]. Notably, SCFAs levels were significantly lower in young and elderly AMI patients than in the healthy control group, suggesting that SCFAs depletion may contribute to the pathophysiology of AMI, and SCFAs levels may serve as diagnostic markers [65].

In experimental models, SCFAs supplementation was reported to significantly improve physiological outcomes and increase survival rates after AMI [66]. For instance, butyrate has demonstrated the ability to alleviate heart failure by reducing systemic inflammation, while propionate supplementation in ApoE-deficient mice has been linked to reductions in vascular inflammation, atherosclerotic plaque burden, and blood pressure [67]. Additionally, recent studies suggest that propionate can reduce atherosclerosis by lowering total cholesterol and LDL levels in human and animal models [68]. Mechanistically, acetate has been found to inhibit the production of pro-inflammatory cytokines IL-6 and IL-8 by activating GPR41/43 receptors[69], while butyrate suppresses NOX2 expression and ROS production in endothelial cells via the PPARδ/miR-181b pathway, thereby improving endothelial function and reducing atherosclerosis risk [70].

Beyond cardiovascular health, SCFAs also support gut integrity by serving as an energy source for intestinal epithelial cells, thereby enhancing gut barrier function. This helps to mitigate “leaky gut” syndrome, which can reduce chronic endothelial inflammation induced by LPS and contribute to cardiovascular diseases [71].

These findings offer promising insights into the role of SCFAs in inhibiting atherosclerosis development and stabilizing plaques during cardiovascular events. However, the current body of evidence, particularly data from human studies, is limited. Therefore, further research is needed to better understand the precise functions and mechanisms of SCFAs in the context of cardiovascular disease.

4.1.3. SCFAs: Role in Diabetic Retinopathy

Studies have shown that SCFAs may cross the blood-retinal barrier via systemic circulation, suggesting that the previously described gut-retinal axis could influence retinal health [72]. For instance, one study demonstrated that butyrate improved retinal pathology in diabetic mice by inhibiting retinal microglial activation, reducing inflammation and neurodegeneration, which are critical processes in the progression of DR [73]. Another study found that butyrate could modulate intestinal and retinal health by inhibiting the expression of claudin-2 in the intestine, a tight junction protein associated with increased intestinal permeability. This inhibition, combined with the upregulation of anti-inflammatory cytokine IL-10, helped repair retinal vascular abnormalities and improve the inflammatory environment in diabetic mice by downregulating NF-κB activity, a key pro-inflammatory signaling pathway [74]. These findings suggest that SCFAs may have both local and systemic anti-inflammatory effects that can contribute to the prevention and treatment of DR.

However, despite these promising results, the exact mechanisms by which SCFAs and other gut-derived metabolites influence retinal pathology remain unclear. Further research is needed to elucidate the precise pathways involved, particularly to understand how gut microbiota-derived SCFAs interact with the BRB and retinal cells. This could provide critical insights into new therapeutic strategies targeting the gut-retinal axis to prevent or treat diabetic retinopathy.

4.1.4. SCFAs: Role in Diabetic Nephropathy

Several studies have highlighted the beneficial effects of SCFAs in DN. For example, acetate has been shown to inhibit renal inflammation and fibrosis in DN by activating G protein-coupled receptors GPR43 and GPR109A [75]. Additionally, butyrate has been demonstrated to suppress inflammatory markers in the kidneys of db/db mice by modulating the miR-7a-5p/P311/TGF-β1 signaling pathway, thereby reducing kidney fibrosis in DN models [76]. Another study indicated that butyrate may improve symptoms of DN by influencing mitochondrial metabolism through the AMPK/Sirt1/PGC-1α signaling pathway [77]. Within certain concentration ranges, butyrate supplementation has also been found to alleviate hyperglycemia-induced oxidative stress and inflammatory damage in mesangial cells, which is critical to the development of DN.

In addition to SCFAs supplementation, other substances, including graminan-type fructan from Achyranthes bidentata [78], dietary fibers [75], inulin-type fructans [79], peony polysaccharides [80], Hong Guo Ginseng Guo [81], punicalagin [82], and resveratrol [83], have been shown to promote the generation of SCFAs and SCFAs-producing bacteria. These substances help mitigate inflammation in tubular and podocyte cells, regulate glucose metabolism, inhibit kidney fibrosis, and modulate the NLRP3 inflammasome, all of which modulate DN progression.

In summary, regulating the gut microbiota-SCFAs axis represents a promising therapeutic direction for managing diabetic nephropathy. Further research is needed to elucidate the full scope of SCFAs' therapeutic potential, particularly in human clinical studies.

4.2. Bile Acids

Bile acids are the primary components of bile, synthesized in the liver. Once primary bile acids enter the intestine, they are converted into free bile acids through the action of intestinal bacterial bile salt hydrolases. This is followed by 7α-dehydroxylation, transforming them into secondary bile acids. These secondary bile acids can then return to the liver via the enterohepatic circulation, with a small amount entering the bloodstream. Bile acids can directly or indirectly modulate the composition of gut microbiota by activating intestinal innate immune genes. They also interact with the liver farnesoid X receptor (FXR) and bile acid G protein-coupled receptor 5 (TGR5), modulating glucose metabolism and exerting anti-inflammatory effects. In summary, research has shown that bile acids play a significant role in regulating cardiovascular complications associated with diabetes.

4.2.1. BAs: Role in Ischemic Stroke

Charach et al. reported that higher fecal concentrations of deoxycholic acid (DCA), lithocholic acid (LCA), and cholic acid (CA) were associated with improved survival rates following stroke [84]. A metabolomic analysis of young stroke patients without common risk factors further revealed significantly elevated serum glycochenodeoxycholic acid (GCDCA) levels in the stroke group compared to healthy controls, suggesting that specific bile acids may be involved in stroke pathophysiology [85]. Additionally, epidemiological studies have demonstrated that total bile acid (TBA) levels in patients with acute ischemic stroke (AIS) are negatively correlated with mortality rates [86]. Collectively, these findings suggest that bile acids may have predictive potential for stroke outcomes, possibly through interactions with specific bile acid receptors, such as TGR5.

TGR5, a novel membrane-bound bile acid receptor, is found in neurons, microglia, and astrocytes, and its activation has been linked to neuroprotective effects in several models [87]. For instance, TGR5 activation attenuates microglial activation, reducing the production of pro-inflammatory cytokines in models of hepatic encephalopathy, a process that may have parallels in stroke-induced neuroinflammation [88]. Furthermore, studies in mice indicate that administering ursodeoxycholic acid (UDCA) inhibits NLRP3-associated pro-inflammatory cytokines via the TGR5/PKA pathway, leading to reduced infarct size and improved neurological outcomes following stroke [89]. These results suggest that bile acids, via TGR5, might regulate inflammation and accelerate the recovery after ischemic stroke.

Emerging evidence also highlights the role of gut microbiota in modulating bile acids. One study has demonstrated that colestimide resin alleviates cerebral ischemic injury in obese mice by improving gut microbiota dysbiosis and modulating bile acid profiles [90]. Similarly, the combination of Astragalus and safflower has shown neuroprotective effects in rats with cerebral ischemia/reperfusion injury (CI/RI), potentially by regulating gut microbiota, activating FXR, and maintaining bile acid homeostasis. This treatment was associated with reduced Th17 cells in the brain, increased Treg cells, lowered pro-inflammatory cytokine IL-17A levels, and enhanced anti-inflammatory cytokine IL-10 levels [91]. These changes contributed to reduced neuroinflammation, preserved blood-brain barrier integrity, and improved outcomes in CI/RI.

4.2.2. BAs: Role in Coronary Heart Disease

Previous studies have indicated that multiple bacterial species, including *Lactobacillus*, *Bifidobacterium*, *Bacteroides*, and *Enterococcus*, participate in the complex biotransformation of Bas [92]. For instance, Zhou et al. found that levels of intestinal *Lactobacillus* in patients with AMI are associated with inflammatory responses and cardiovascular events [93]. Moreover, decreases in serum TBA and *Lactobacillus* levels in AMI patients have been independently correlated with increased risks of CAD, all-cause mortality, and cardiovascular mortality [94]. Lam et al. further demonstrated that supplementation with *Lactobacillus plantarum 299v* can mitigate acute myocardial injury following ischemia-reperfusion, suggesting its potential cardioprotective role [95].

Research also indicates that the composition and pool size of bile acids change significantly in patients with CAD. A recent small cohort study reported that decreased bile acid excretion is linked to increased risks of atherosclerosis and CAD [84]. Additionally, in patients diagnosed or suspected of having CAD, lower TBA levels have been independently associated with the severity of coronary artery lesions, highlighting the potential role of bile acids as biomarkers for cardiovascular disease [96]. Zhang et al. explored the specific cardioprotective mechanisms of bile acids in animal models. Their research showed that bile acids can induce cardioprotective changes and improve the response of cardiac muscle to physiological, inotropic and hemodynamic stress in mice. Elevated bile acid levels may have diverse effects on the function and metabolism of cardiomyocytes, vascular endothelial cells, and vascular smooth muscle cells. The mechanisms involved primarily include reducing endothelin-1 expression and modulating both iNOS and eNOS to facilitate vasodilation [97]. Additionally, bile acids have been shown to mediate the relationship between gut microbiota dynamics and cardiovascular health by influencing circulating lipids, inflammation, and glucose regulation [98]. Consequently, the distribution and concentration of circulating bile acids are being explored as potential therapeutic targets for AMI and other cardiovascular conditions [99].

In conclusion, further investigations into the mechanisms of bile acids, particularly their effects on inflammatory and metabolic pathways, to clarify their specific roles in CHD.

4.2.3. BAs: Role in Diabetic Retinopathy

Metabolomic studies have revealed a significant reduction in serum chenodeoxycholic acid (CDCA) in Chinese patients with type 2 diabetes during the progression of DR [100]. However, few studies have explored the specific role of CDCA in DR, necessitating further investigation. In contrast, the roles of UDCA and TUDCA in DR have been more extensively studied. Research suggests that intermittent fasting can stimulate TUDCA synthesis by reshaping the gut microbiome, potentially offering a protective effect against diabetic retinopathy [101]. TUDCA exerts its protective effects on the retina primarily by activating TGR5, a bile acid receptor [101].

Meta-analysis results have demonstrated that TUDCA effectively delays retinal neuron degeneration and apoptosis in both in vitro and in vivo models, helping to preserve retinal structure and function [102]. This protective effect might be due to the TUDCA's ability to inhibit apoptosis, reduce inflammation, alleviate oxidative stress, suppress ER stress, and decrease angiogenesis [101]. Specifically, TUDCA protects human retinal microvascular endothelial cells from dysfunction induced by high glucose and mitigates damage in streptozotocin-induced DR models in rats. The mechanisms behind these effects involve the reduction of NO levels and the downregulation of the expression of ICAM-1, NOS, NF-κB p65, and VEGF [103].

In addition to TUDCA, studies have shown that UDCA can reduce macrophage expression in the retina, particularly in APB5-induced models, and also decrease angiogenic factors and inflammatory mediators [104]. These findings suggest that bile acids such as TUDCA and UDCA could be valuable in preventing and treating diabetic retinopathy by targeting key pathways involved in inflammation, oxidative stress, and angiogenesis.

4.2.4. BAs: Role in Diabetic Nephropathy

A clinical study identified elevated bile acids as an independent risk factor for adverse renal outcomes in patients with diabetic kidney disease, and recommended that serum bile acid levels should be maintained above 2.8 mmol/L [105]. Additionally, an in vivo study demonstrated that a novel polymeric phosphate and bile acid chelator, SAR442357, could delay the progression of diabetic kidney disease in rat models [106]. In parallel, treatment with UDCA and TUDCA has been shown to reduce the expression of sodium-glucose co-transporter 2 and oxidative stress in rodent models of diabetic nephropathy. These bile acids prevented podocyte apoptosis induced by endoplasmic reticulum stress, contributing to renal protection [107–110]. Moreover, studies have confirmed that bile acid derivatives or analogs interact with bile acid receptors (TGR5/FXR) in the kidneys, exerting renal protective effects [31,111].

Furthermore, several natural compounds, such as QiDiTangShen granules [112], Magnesium lithospermate B [113], and corn silk polysaccharides [114], have been found to modulate gut microbiota composition and improve bile acid profiles in diabetic nephropathy mouse models. These interventions potentially protect renal function by enhancing bile acid metabolism and reducing inflammatory markers. For example, the oral administration of nanoscale bile acids containing mesosulfobutylated epoprostenol reduced the expression of angiotensin II type 1 receptor, inducible nitric oxide synthase, and transforming growth factor-β1, demonstrating significant protective effects on renal function in Wistar rats [115].

4.3. TMAO

TMAO is primarily formed through the intestinal metabolism of dietary sources such as choline, carnitine, or choline-containing compounds, which are converted to trimethylamine (TMA) in the gut. TMA can either be utilized by intestinal methanogenic bacteria to produce methane or absorbed by the intestinal wall. Once absorbed, TMA is oxidized in the liver by flavin-containing monooxygenases FMO1 and FMO3, resulting in the production of TMAO [116]. Consequently, both the intake of TMA precursors and the gut microbiota composition influence TMAO production [117].

Numerous studies have highlighted the role of TMAO in promoting inflammation, oxidative stress, and endothelial dysfunction, all of which are critical contributors to diabetic vascular complications. Elevated TMAO levels correlates with an increased risk of atherosclerosis, impaired vascular repair, and overall cardiovascular disease in patients with diabetes. These findings suggest that TMAO not only serves as a biomarker for metabolic disorders but may also play a direct role in the progression of diabetic vascular complications, making it a potential target for therapeutic interventions.

4.3.1. TMAO: Role in Ischemic Stroke

In a large-scale clinical study, elevated plasma TMAO levels were associated with an increased risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death [118]. Transplanting fecal microbiota from human subjects with low and high TMAO production into germ-free mice led to increased brain infarct size and more severe functional impairments following stroke, particularly after choline supplementation and TMAO exposure [119]. These findings suggest a potential link between TMAO and IS, though the precise mechanisms remain unclear.

Several studies have begun to elucidate the pathways through which TMAO may contribute to cardiovascular diseases and stroke. Koeth et al. demonstrated that dietary intake of TMAO precursors, such as choline or L-carnitine, promotes microbial-dependent atherosclerosis in mice by inhibiting reverse cholesterol transport, reducing the total hepatic bile acid pool, and decreasing the expression of intestinal cholesterol transport proteins [120]. These changes in cholesterol metabolism can exacerbate atherosclerosis, a major risk factor for ischemic stroke. In addition, Wang et al. found that TMAO enhances foam cell formation by upregulating the expression of two macrophage scavenger receptors, CD36 and SR-A1, both of which are associated with atherosclerosis progression [121].

Further supporting this link, Seldin et al. confirmed that TMAO activates the MAPK and NF-κB pathways, promoting vascular inflammation and enhancing leukocyte recruitment to endothelial cells in mice [122]. Additionally, TMAO has been shown to stimulate the generation of IP3 in platelets, triggering intracellular $Ca2^{+}$ release and promoting platelet activation, which may increase the risk of thrombosis [123].

In summary, TMAO may serve as both a biomarker and a potential therapeutic target for preventing stroke and other cardiovascular events.

4.3.2. TMAO: Role in Coronary Heart Disease

Numerous clinical studies have indicated a strong correlation between elevated TMAO levels and an increased risk of coronary artery atherosclerosis, heart failure, and myocardial infarction [124–126]. As early as 2011, Hazen and his team first established this link, demonstrating that higher plasma TMAO levels were associated with greater cardiovascular risk [121]. They further showed that dietary supplementation with choline or TMAO promoted atherosclerosis in mice [120]. Building on these findings, a 2015 study revealed that the natural compound 3,3-dimethyl-1-butanol (DMB) inhibits microbial choline TMA lyase, thereby reducing plasma TMAO levels in mice and preventing the development of atherosclerotic lesions [127].

In addition to its role in promoting atherosclerosis, recent research has shown that TMAO increases the risk of platelet hyperactivity and thrombosis [123], which are key contributors to both coronary heart disease (CHD) and myocardial infarction. Chen et al. expanded our understanding by identifying the first TMAO receptor, PERK, and proposing that the TMAO/PERK pathway is integral to the pathogenesis of liver insulin resistance and

metabolic syndrome [128]. This suggests that elevated TMAO levels may also contribute to broader metabolic dysfunction.

A decade-long prospective study further demonstrated that sustained elevated TMAO levels are linked to an increased risk of CHD, indicating that diet could modify this relationship [129]. Mechanistic studies have elucidated how TMAO regulates bile acid synthesis and cholesterol metabolism, both of which drive AS development [130]. Specifically, TMAO upregulates the expression of macrophage scavenger receptors, CD36 and SR-A1, promoting foam cell formation and accelerating the progression of AS and CHD [131]. These findings underscore the multifaceted role of TMAO in cardiovascular disease pathogenesis.

Furthermore, TMAO promotes vascular inflammation and oxidative stress through several key pathways. In the vascular intima and adventitia, TMAO regulates ROS levels via the SIRT1/AMPK signaling pathway, contributing to endothelial dysfunction [132]. Simultaneously, TMAO activates the MAPK and NF-κB signaling pathways in vascular endothelial and smooth muscle cells, exacerbating inflammation. TMAO also stimulates the NLRP3 inflammasome, further inducing ROS production and impairing reverse cholesterol transport, which together accelerate atherosclerosis progression [133].

In summary, these interconnected pathways underscore the importance of TMAO as both a biomarker and potential therapeutic target for managing CHD in diabetic patients.

4.3.3. TMAO: Role in Diabetic Retinopathy

A hospital cross-sectional study found that patients with diabetic retinopathy (DR) had significantly higher plasma TMAO levels compared to those without DR, and these levels were correlated with the severity of DR [134]. While this association is compelling, prospective cohort studies are essential to establish causality between elevated TMAO levels and DR progression.

In vitro studies suggest that TMAO can exacerbate high-glucose-induced dysfunction in human retinal microvascular endothelial cells (HRMECs) by accelerating NLRP3 inflammasome activation. Additionally, TMAO has been shown to enhance HRMECs proliferation, wound healing, migration, tube formation, and degradation of intercellular tight junctions under high-glucose conditions, contributing to the breakdown of the retinal barrier [135]. These findings suggest that TMAO may play a role in DR pathology by promoting vascular dysfunction and inflammation. Future research should focus on in vivo studies to clarify the precise mechanisms through which TMAO contributes to DR damage.

4.3.4. TMAO: Role in Diabetic Nephropathy

In patients with type 2 diabetes, elevated levels of TMAO in the blood are associated with a doubling of serum creatinine levels and an increased risk of progressing to end-stage kidney disease and mortality [136]. These findings suggest that TMAO could serve as a potential biomarker for renal function decline and mortality in type 2 diabetes. Similarly, in patients with type 1 diabetes, higher plasma TMAO concentrations have been linked to increased mortality, cardiovascular events, and adverse renal outcomes [137]. Mechanistically, TMAO can activate renal inflammation, oxidative stress, fibrosis, and endothelial dysfunction, all of which contribute to the pathogenesis of diabetic nephropathy (DN) [138,139].

Although studies suggest that gut microbiota may influence TMAO production, there is currently no direct evidence demonstrating a causal link between specific intestinal bacteria and the development of DN via TMAO. More research is needed to explore how gut microbiota modulates TMAO levels and whether targeted interventions in the gut-kidney axis could mitigate the progression of DN.

4.4. Others

4.4.1. 2-methylbutyrylcarnitine

Acylcarnitine is an intracellular compound synthesized primarily from the combination of carnitine and fatty acid acyl groups. Its primary function is to facilitate the transport of fatty acids into mitochondria, where they undergo oxidation to generate energy [140]. Elevated levels of various acylcarnitines, such as 2-methylbutyrylcarnitine (2MBC), isobutyrylcarnitine, and hexanoylcarnitine, have been observed in the plasma of patients with metabolic disorders, including obesity, diabetes, and hypertension [141–143].

Recent research has highlighted the potential role of acylcarnitines, particularly 2MBC, in increasing the risk of thrombosis. In their study, Huang et al. found that short-chain and medium-chain acylcarnitines, especially 2MBC, may significantly contribute to platelet hyperreactivity, which is linked to thrombosis risk [144]. This study reveals that gut microbioita produce acylcarnitines. Specifically, 2MBC was shown to enhance platelet

hyperreactivity via the integrin α2β1 pathway, thus increasing the risk of thrombosis. These findings suggest that 2MBC could serve as a potential target for cardiovascular disease intervention.

4.4.2. Amino Acid-Derived Metabolites

Numerous studies have demonstrated that the gut microbial metabolism of aromatic amino acids produces metabolites potentially linked to cardiovascular complications in diabetes. For example, the gut microbial metabolite phenylacetylglutamine (PAGln), derived from phenylalanine (Phe), has been strongly associated with CVD via adrenergic receptor signaling [145,146]. PAGln has been shown to enhance the activation of both whole blood platelets and ex vivo platelets, thereby promoting thrombosis in mice. Specifically, PAGln signals directly to platelets via G protein-coupled α2a-adrenergic, α2b-adrenergic, and β2-adrenergic receptors, leading to increased platelet aggregation and thrombosis in vivo [68].

In addition to PAGln, gut microbes metabolize other aromatic amino acids, such as tyrosine (Tyr) and tryptophan (Trp), into precursors of known uremic toxins, including p-cresyl sulfate (pCS) and indoxyl sulfate (IS) [147]. These metabolites increase cardiovascular mortality, particularly in patients with impaired renal function. Studies have shown that both pCS and IS can enhance platelet reactivity by increasing P-selectin expression, promoting the formation of platelet microparticles, and enhancing platelet-monocyte aggregates, contributing to thrombosis in animal models of vascular injury [148–150].

Notably, while many of these microbial metabolites are associated with negative cardiovascular outcomes, some, such as indole-3-propionic acid (I3PA), have been reported to reduce the risk of diabetes, suggesting a nuanced role of gut-derived metabolites in metabolic health [151].

A large cohort study involving more than 4000 participants further supports the significant impact of gut bacterial metabolites on cardiovascular health. This study found that various metabolites derived from aromatic amino acids, such as phenylacetylglutamine, phenylacetylglycine, p-cresyl sulfate, p-cresyl glucuronide, 4-OH-benzoic acid, 4-OH-mandelic acid, indole glucuronide, and indoxyl sulfate, were associated with an increased risk of major adverse cardiovascular events, including myocardial infarction, stroke, and death, as well as overall mortality [152].

In conclusion, these findings highlight the complex role of gut-derived metabolites in cardiovascular health and disease. Further research is necessary to elucidate the specific mechanisms through which these aromatic amino acid metabolites influence cardiovascular outcomes, potentially offering novel therapeutic targets.

Table 2. Sources, mechanisms, and effects of key metabolites in vascular complications.

Metabolites	Sources	Mechanisms	Effects	Ref.
SCFAs	Dietary fiber	Interacted with GPCRs on intestinal epithelial cells, such as GPR41, GPR43, and GPR109A.	Regulate inflammation, improve blood-brain barrier integrity, reduce vascular and renal inflammation, and protect retinal health	[53,55,63]
BAs	Cholesterol is synthesized in the liver and converted into secondary BAs by gut bacteria	Interacted with the liver FXR and bile acid TGR5	Reduce inflammation, protect cardiac and renal function, and delay retinal neuron degeneration.	[84,89]
TMAO	Choline, phosphatidylcholine and L-carnitine	Activated the NF-κB pathway, NLRP3 inflammasome, and endoplasmic reticulum stress response, leading to the upregulation of tissue factor and vascular cell adhesion molecule-1 in the vascular endothelium.	Promote vascular inflammation, platelet activation, oxidative stress, and endothelial dysfunction, contributing to vascular and renal damage	[120,121,123]

5. Potential Therapeutic Options for Targeting Gut Microbes and Metabolites in Diabetic Vascular Diseases

Restoring a healthy gut microbiome is considered a potential therapeutic approach for mitigating cardiovascular complications associated with diabetes. Moreover, interventions such as prebiotics, probiotics, dietary modifications, and FMT have been shown to reduce harmful circulating metabolites in the host (Table 3).

5.1. Probiotics/Prebiotics

Since 2020, there has been significant academic interest in the role of probiotics, prebiotics, postbiotics, and synbiotics in the treatment of diabetic vascular disease. Probiotics, such as bifidobacteria and lactobacilli, can strongly improve gut microbiota imbalances in patients with metabolic syndrome. These probiotics work by optimizing the gut microbial environment, increasing the abundance of beneficial bacteria, and inhibiting harmful bacteria, which contributes to reducing blood glucose levels, lowering blood lipids and blood pressure, alleviating inflammation, and enhancing insulin sensitivity [153–155].

Several studies have investigated the effects of specific probiotic strains on metabolic parameters in diabetic and obese models. For instance, *Lactobacillus fermentum 296* restored lactobacilli levels in a high-fat diet rat model, significantly improving hyperlipidemia, reducing sympathetic nervous system activity, and lowering systolic blood pressure [156]. Similarly, *Lactobacillus plantarum LB818* demonstrated anti-obesity effects in high-fat diet-induced obese mice, helping to control weight gain and improve body fat distribution and fasting glucose levels, while modulating gut microbiota composition [157]. In patients with T2DM, Bifidobacterium breve significantly impacted blood glucose, blood lipids, and gut microbiota composition. The supplementation group showed reduced levels of BUN, creatinine, LDL, TG, and HbA1c, as well as notable changes in gut microbiota composition [158]. Additionally, strains like *Lactobacillus johnsonii 3121* and *Lactobacillus rhamnosus 86* demonstrated anti-obesity effects in mice by downregulating lipogenesis-related genes and restoring gut microbiota balance to prevent obesity [159].

Prebiotics, as non-absorbable short-chain carbohydrates, are fermented by colonic bacteria, producing SCFAs, particularly butyrate, which has shown preventive effects on diabetes. Research has demonstrated that butyrate-producing bacteria, such as *Faecalibacterium*, *Roseburia*, and *Bacteroides*, are significantly reduced in diabetic mice, correlating with impaired vascular function and heightened inflammation. Further studies have found that administering butyrate-producing bacteria can restore protective microbiota and improve vascular function by activating the Nrf2/HO-1 pathway, suggesting that butyrate may help reduce the risk of developing diabetes [160,161].

In patients with diabetes and CAD, supplementation with probiotics, along with vitamin D or selenium, has been shown to significantly improve markers of psychological well-being and metabolic health. Improvements were observed in high-sensitivity C-reactive protein (hs-CRP), NO, LDL, total cholesterol, and other indicators of inflammation and oxidative stress [162,163]. Additionally, supplementation with a synbiotic containing probiotic strains and the prebiotic inulin improved several health markers, including serum hs-CRP, cholesterol, plasma NO, and malondialdehyde, in patients with CAD [164]. *Lactobacillus plantarum 299v* has also been found to enhance endothelial function and reduce systemic inflammation in these patients [165]. However, despite these promising results thus far, many clinical studies have not specifically examined the impact of probiotics on diabetic vascular pathology, highlighting the need for more targeted research in this area.

In summary, by improving gut microbiota composition, reducing inflammation, and modulating metabolic pathways, these interventions hold promise as effective strategies for managing diabetic vascular disease.

5.2. Diet

Studies have shown that diet is a crucial factor influencing diabetes and cardiovascular diseases by directly affecting blood glucose levels, weight management, and overall metabolic status. Dietary choices not only influence blood parameters but also have a profound impact on gut microbiota, thereby affecting inflammation, oxidative stress, and vascular health.

Studies indicate that reducing branched-chain amino acid (BCAA) intake improves oral glucose sensitivity, highlighting the importance of amino acid balance in glucose metabolism [154]. Additionally, consuming omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from marine fish, significantly enhances metabolic health by improving glucose tolerance and reducing adipose tissue-induced inflammation, thus benefiting cardiovascular health [166]. Ketogenic diets have also been shown to positively affect glucose and lipid metabolism while reducing systemic inflammation, providing protective effects in diabetic mouse models [167].

High-fiber diets are crucial for cardiovascular health, as they promote the production of SCFAs, which modulate key signaling pathways such as GPR43 and GPR109A. Conversely, low-fiber diets negatively impact hypertension and metabolic health due to reduced SCFAs production and impaired signaling [168]. Furthermore, high-fiber intake can prevent myocardial infarction by significantly improving heart function, reducing infarct size, and modulating gut microbiota to decrease inflammation [169].

In addition to macronutrients like fibers and fats, specific micronutrients also contribute to gut and cardiovascular health. Nuts, which contain unsaturated fatty acids, fiber, and polyphenols, provide multiple health benefits. They help regulate blood glucose, control weight, improve gut microbiota composition, and enhance cardiovascular health, demonstrating significant potential for managing diabetes and cardiovascular diseases [170]. Similarly, blueberry supplementation has been shown to reduce vascular inflammation, improve endothelial function, and promote the growth of beneficial microorganisms, further highlighting the role of diet in modulating the gut-vascular axis [171].

In summary, various dietary patterns can directly influence gut microbiota composition and function, which in turn affect systemic inflammation, glucose metabolism, and vascular health. Alterations in gastrointestinal transit time, nutrient availability, and gut pH levels due to dietary changes can lead to shifts in bacterial populations, offering a new strategy for regulating metabolic disorders caused by gut dysbiosis [172]. Consequently, dietary interventions are considered effective therapeutic approaches for managing diabetic vascular complications through gut microbiota modulation.

5.3. Fecal Microbiota Transplantation

FMT, which involves transplanting fecal material from a healthy donor to a recipient to modulate their gut microbiota, is increasingly recognized as an innovative approach for treating various microbiota-related disorders. In the context of T2DM, research indicates that FMT can significantly improve insulin resistance, as measured by HOMA-IR, and reduce BMI in patients. Additionally, FMT has been shown to effectively control fasting glucose, postprandial glucose, and hemoglobin A1c levels, which are key markers of metabolic health. Notably, when FMT is combined with metformin, the successful engraftment of donor microbiota can substantially increase microbial diversity. Specific strains, such as *Chlorobium phaeovibrioides* and *Bifidobacterium adolescentis*, have been negatively correlated with HOMA-IR, suggesting their potential role in improving insulin sensitivity and metabolic control [173].

A double-blind, placebo-controlled study assessed the safety and efficacy of FMT capsules in 22 obese patients without diabetes, non-alcoholic steatosis, or metabolic syndrome. While this study found no significant difference in BMI changes at week 12 between the FMT and placebo groups, it did observe a sustained shift in gut microbiota composition towards that of the donor and a reduction in fecal taurocholic acid levels. However, the impact on GLP-1 levels or BMI was not significant, indicating that the metabolic effects of FMT may vary depending on patient characteristics and treatment duration [174]. This highlights the need for further research to explore the long-term metabolic outcomes of FMT.

Similarly, in another randomized controlled study involving male patients with metabolic syndrome, FMT from lean donors resulted in improved glycemic control at six weeks post-treatment compared to those receiving autologous microbiota, suggesting that the microbiota from lean donors may offer greater metabolic benefits [175]. This study underscores the importance of donor microbiota composition in determining the efficacy of FMT for metabolic health.

Preclinical studies also support the therapeutic effects of FMT in diabetes. For instance, in a diabetic db/db mouse model, FMT treatment increased the abundance of beneficial bacterial taxa, such as *Ruminococcaceae* and *Porphyromonadaceae*, restored gut barrier integrity and reduced inflammation levels [176]. In a diabetic nephropathy model using BTBR ob/ob mice, FMT not only reduced weight gain but also improved insulin resistance and inflammatory markers, which were closely associated with an increased abundance of *Odoribacteraceae* bacteria [177]. These preclinical results suggest that the modulation of gut microbiota through FMT may help alleviate both systemic and gut-specific inflammation, further contributing to metabolic improvements.

Although existing studies have provided encouraging results, particularly regarding FMT in controlling blood glucose, weight, and inflammation, as well as reducing insulin resistance, preclinical studies have also revealed that intestinal flora plays a significant role in the development of vascular lesions. However, there is still a lack of clinical studies evaluating the specific effects of FMT on vascular function in patients.

5.4. Other Strategies

In microbiota metabolite research, specific gut bacteria-derived enzymes, such as dipeptidyl peptidase-4 (DPP4), have been shown to lower active GLP-1 levels, thereby affecting glucose metabolism and contributing to diabetes progression. High-throughput screening has identified daurisoline-d4 (Dau-d4) as a potent DPP4 inhibitor, which improves glucose tolerance in diabetic mice by enhancing GLP-1 activity and increasing insulin sensitivity [4]. Similarly, the natural compound AT-I has demonstrated protective effects in gestational diabetes mellitus mouse

models by reversing high glucose-induced increases in ROS and alleviating glucose dysregulation and fetal heart abnormalities [178].

In addition to pharmacological treatments, traditional herbal medicines and natural compounds have gained attention for their potential in managing diabetes and cardiovascular diseases, often through the modulation of the gut microbiota. The traditional Chinese medicine formula Ginseng and Astragalus Decoction, which contains ginseng, Atractylodes macrocephala, and other herbs, has been shown to lower blood glucose levels and protect against myocardial injury in mouse models. This formula promotes the growth of beneficial gut bacteria while inhibiting pathogenic microorganisms, leading to improvements in metabolic cardiomyopathy [179]. Another herbal formula, ZGJTSXF, has been found to inhibit cardiomyocyte apoptosis and reverse microbial imbalances, specifically increasing the abundance of beneficial taxa such as *Lactobacillus*, *Alloprevotella*, and *Alistipes*, which are linked to improved cardiovascular health [180].

Moreover, compounds such as eugenol, paeoniflorin, and myricetin have demonstrated anti-atherosclerotic properties, improving cardiac function and reducing cardiomyocyte hypertrophy and fibrosis. Despite these promising effects, our understanding of how traditional Chinese medicines influence gut microbiota remains limited. Further research is needed to elucidate the mechanisms through which these treatments modulate microbial composition and how these changes enhance therapeutic efficacy [181–183].

Table 3. Therapeutic strategies targeting gut microbiota and their metabolites.

Methods	Subjects	Therapies	Conclusions	Ref.
flora	HFD mice	*Lactobacillus fermentum 296 LB818*, administered orally for 8 weeks	alleviated hyperlipidemia	[156]
flora	HFD mice		alleviated obesity and hepatic steatosis	[157]
flora	T2DM patients	*Bifidobacterium breve*	relieved metabolic disorders	[158]
flora	HFD mice	*Lactobacillus johnsonii 3121* and *Lactobacillus rhamnosus 86*, administered orally for 12 weeks	improved blood lipid levels and prevented obesity	[159]
flora	db/db mice	*Clostridium butyricum*, administered orally every two days for 2 months	alleviated vascular disease by activating the Nrf2/HO-1 pathway	[161]
diet	T2DM patients	lacking BCAAs	reduced postprandial insulin secretion, improved white adipose tissue metabolism	[154]
diet	HFD mice	marine fish rich in omega-3	improved blood glucose tolerance, reduced inflammation in fat tissue	[166]
diet	ApoE-/- mice	a ketogenic diet for six months	reduced aortic atherosclerosis and aortic calcification, improved intestinal barrier	[167]
diet	caco-2 cells	Nuts	reduced serum cholesterol	[170]
diet	db/db mice	intermittent fasting diet	prevented diabetic retinopathy	[101]
diet	db/db mice	a diet containing 3.8% freeze-dried blueberries for 10 weeks	induced EC endothelial inflammation	[171]
FMT	T2DM patients	FMT alone and in combination with metformin	improved metabolic health, reversed insulin resistance	[173]
FMT	db/db mice	FMT	restored intestinal barrier	[176]
FMT	db/db mice	FMT	improved inflammation and insulin resistance	[177]
Other strategies	DCM mice	Ginseng fungus Dingzhi decoction	reduced blood sugar levels and protected cardiac tissue	[179]
Other strategies	DCM mice	Zuogui Jiangtang Shuxin formula	improved heart function, inhibited apoptosis of cardiomyocytes	[180]
Other strategies	DCM mice	crocin probiotics	reduced oxidative stress, inflammation, and apoptosis	[184]
Other strategies	DCM mice	geraniol	reduced the risk of atherosclerotic disease	[181]
Other strategies	PGDM mouse model	AT-I	alleviated blood glucose problems and abnormal fetal heart development	[178]
Other strategies	DCM mice	Paeoniflorin	alleviated myocardial damage	[182]
Other strategies	DCM mice	Myricetin	prevented the development of DCM	[183]

Recent studies exploring combination therapies have shown the advantages of synergistic treatment strategies. For example, one study combined dapagliflozin (a pharmacological SGLT2 inhibitor), saffron-derived prebiotics, and probiotic strains such as *Lactobacillus* and *Bifidobacterium*. This tri-therapy significantly reduced oxidative stress, inflammation, and apoptosis induced by streptozotocin (STZ) in diabetic models, while also restoring the

balance of symbiotic gut microbiota. The findings suggest that combining saffron with lactobacilli may be effective treatments for diabetic cardiomyopathy [184].

In conclusion, these therapeutic strategies, integrating conventional pharmacological treatments with natural remedies, show considerable potential for improving outcomes in diabetes and cardiovascular diseases. By modulating gut microbiota and enhancing metabolic functions, these combined approaches offer novel avenues for clinical treatment. These findings provide crucial theoretical and practical ideas that may guide future development of therapeutic interventions targeting gut microbiota for diabetic complications management.

6. Summary and Discussion

In this review, we summarize the mechanisms and roles of gut microbiota and their metabolites, such as SCFAs, BAs, and TMAO, etc, in the regulation of cardiovascular complications in diabetes. These metabolites not only influence cardiovascular health by affecting endothelial function and inflammatory responses but are also closely linked to glucose, lipid, and energy metabolism. The concept of the "gut-vascular interaction axis" provides a better understanding of how gut microbiota impacts diabetes-related vascular complications through immune modulation, metabolic byproducts, and neural signaling pathways.

Traditional exogenous insulin injection methods often fail to provide precise blood glucose control, requiring lifelong dependence on insulin therapy. Long-term poor glucose management can lead to numerous complications, including cardiovascular diseases, nephropathy, retinopathy, and more. Additionally, improper insulin use may result in life-threatening hypoglycemic events [185]. Emerging strategies for diabetes treatment, viewed through the lens of gut microbiota, include targeted probiotic delivery, pasteurization and application of live bacteria, fecal microbiota transplantation, and the use of genetically modified microorganisms. Given the strong relationship between the type and abundance of gut microbiota and dietary factors, we anticipate that future interventions focusing on regulating gut microbiota and its metabolites—such as short-chain fatty acids and imidazole propionate—through dietary adjustments could provide a simpler, safer, and more effective approach for the prevention and treatment of T2DM.

Despite significant progress, several unresolved questions and challenges remain in understanding the role of gut microbiota and their metabolites in diabetes. Current research often relies on observational data and animal models, limiting the ability to establish causal relationships and fully replicate human disease conditions. Human studies frequently face small sample sizes, a lack of longitudinal data, and variability in participant characteristics, such as diet, lifestyle, and genetics, which hinder generalizability and translational potential. Additionally, while metabolites like SCFAs and TMAO have been implicated in diabetic complications, the precise molecular mechanisms through which they influence metabolic and vascular pathways are unclear, requiring further exploration of their interaction with host immune and vascular systems. Inter-individual variability in gut microbiota composition, influenced by genetics, diet, and environmental factors, adds another layer of complexity, emphasizing the need for personalized medicine.

To address these challenges, integrating multi-omics technologies, such as metabolomics, genomics, and proteomics, with microbiota data offers a promising path forward. This approach can unravel complex microbiota-host interaction networks and identify key metabolites linked to disease progression. Advances in bioinformatics and machine learning further support the development of personalized microbiome-based interventions by enabling the identification of microbiota signatures specific to diabetes subtypes or complications. Additionally, large-scale longitudinal cohort studies, coupled with improved humanized animal models, can enhance our understanding of microbiota dynamics and bridge the gap between preclinical findings and clinical application. Translational research focusing on microbiota-targeted therapies, including probiotics, prebiotics, and microbiota-derived metabolites, as well as emerging technologies like engineered probiotics and small-molecule inhibitors, represents a promising avenue for developing innovative treatments for diabetes and its complications.

Overall, the regulatory role of gut microbiota and their metabolites in diabetes and its complications provides a new perspective for disease management. In the future, developing innovative microbiome-based therapeutic strategies, combined with multi-omics approaches and personalized interventions, is expected to improve the prevention and treatment of diabetes and its complications, ultimately improving patients' quality of life.

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