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Gut Microbiota-Derived Metabolites Orchestrate Metabolic Reprogramming in Diabetic Cardiomyopathy: Mechanisms and Therapeutic Frontiers

Jing-yu Jin[1] | Xin-yu Yang[1] | Ru Feng[2] | Meng-liang Ye[2] | Hui Xu[2] | Jing-yue Wang[1] | Jia-chun Hu[2] | Heng-tong Zuo[2] | Jin-yue Lu[2] | Jian-ye Song[2] | Yi Zhao[2] | Yan Wang[2] | Qian Tong[1]

[1]Department of Cardiovascular Medicine, The First Hospital of Jilin University, Changchun, China | [2]State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence: Yan Wang (wangyan@imm.ac.cn) | Qian Tong (tongqian@jlu.edu.cn)

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Keywords: diabetic cardiomyopathy | epigenetic regulation | gut microbiota | inflammation and oxidative stress | metabolic reprogramming | microbial metabolites

ABSTRACT

Diabetic cardiomyopathy (DCM) is a major cardiovascular complication of diabetes mellitus, characterized by myocardial structural and functional abnormalities in the absence of overt coronary artery disease or hypertension. A growing body of evidence implicates the gut microbiota and its metabolites as key modulators of systemic metabolic homeostasis, influencing energy metabolism, inflammation, and oxidative stress. The gut microbiota emerges as a novel regulator of cardiac remodeling and metabolic reprogramming in DCM through the gut–heart axis. This review aims to synthesize current mechanistic insights into how gut microbiota and its bioactive metabolites contribute to metabolic reprogramming in DCM. It further evaluates the potential of microbiota-targeted interventions as emerging therapeutic strategies to mitigate disease progression and restore cardiac homeostasis. A narrative, mechanistically focused literature review was conducted using PubMed and Web of Science databases. It covered experimental, preclinical, and translational studies up to April 2025. Articles were selected based on relevance to gut microbial metabolism, host cardiac metabolic pathways, and therapeutic interventions linked to DCM. Gut microbiota-derived metabolites—including short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), bile acids, lipopolysaccharides (LPS), tryptophan catabolites, and hydrogen sulfide—modulate cardiometabolic pathways via epigenetic regulation, altered energy substrate utilization, inflammatory signaling, and mitochondrial oxidative stress. These metabolites influence insulin resistance, lipid accumulation, mitochondrial dynamics, and cardiac fibrosis. Therapeutic strategies such as dietary modulation, probiotics, prebiotics, fecal microbiota transplantation, and drugs like SGLT2 inhibitors and GLP-1 receptor agonists have shown promising effects in modulating gut microbiota composition and alleviating DCM phenotypes in animal models. However, clinical evidence remains limited. The gut microbiota plays a pivotal role in the

Abbreviations: AGEs, advanced glycation end-products; BCAA, branched-chain amino acid; BDH1, 3-hydroxybutyrate dehydrogenase 1; CVD, cardiovascular disease; DCM, diabetic cardiomyopathy; FGF21, fibroblast growth factor 21; FMT, fecal microbiota transplantation; GLP-1, glucagon-like peptide 1; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, insulin resistance; KD, ketogenic diet; SCFA, short-chain fatty acid; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T1D, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TMAO, trimethylamine N-oxide.

pathogenesis and potential treatment of DCM through its ability to reprogram host metabolism and inflammation. While preclinical data are compelling, further translational research—including humanized models and multi-omics integration—is required to validate microbiota-targeted therapies for cardiovascular applications. Targeting the microbiota–metabolite axis offers an innovative therapeutic avenue for personalized intervention in diabetic heart disease.

1 | Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by sustained hyperglycemia resulting from impaired insulin secretion, reduced insulin sensitivity, or a combination of both mechanisms [1]. The Global Burden of Disease study estimates that by 2050, approximately 1.31 billion individuals worldwide will be affected by diabetes, underscoring its growing public health burden [2]. The morbidity and mortality associated with diabetes are largely attributable to its vascular complications, which include both macrovascular and microvascular diseases [3]. Among these, cardiovascular disease (CVD) represents the leading cause of death and disability in diabetic populations, significantly diminishing quality of life and longevity [4]. Diabetic cardiomyopathy (DCM) is recognized as a distinct clinical entity within diabetic cardiovascular complications, initially defined as myocardial dysfunction occurring independently of hypertension, coronary artery disease, or valvular abnormalities. DCM typically begins with diastolic dysfunction, which is characterized by impaired myocardial relaxation and increased ventricular stiffness. This is often attributed to myocardial fibrosis, interstitial collagen deposition, and microvascular dysfunction driven by chronic hyperglycemia, insulin resistance, and inflammation [5]. These metabolic disturbances impair calcium handling and reduce myocardial compliance, resulting in delayed ventricular filling. As the disease progresses, persistent oxidative stress, lipotoxicity, and mitochondrial dysfunction further compromise cardiomyocyte contractility, ultimately culminating in systolic impairment and overt heart failure. This progression from diastolic to systolic dysfunction reflects the cumulative effect of metabolic, structural, and inflammatory stressors associated with diabetes [6–8].

Recent experimental and clinical research has elucidated several molecular mechanisms underlying DCM, including oxidative stress [9, 10], defective insulin signaling [11], mitochondrial dysfunction [12], impaired autophagy [13], ferroptosis [14, 15], necroptosis, and apoptosis [16, 17]. Despite advances in glycemic control and pharmacological interventions—such as angiotensin-converting enzyme inhibitors—these treatments primarily delay progression and fail to reverse established myocardial injury. This limitation highlights the critical need for novel, mechanism-based therapeutic strategies targeting the underlying metabolic and cellular dysfunction in DCM.

Metabolic reprogramming—a hallmark of failing myocardium—refers to adaptive alterations in cellular metabolism in response to pathological stress. In the context of DCM, this includes a shift in energy substrate utilization, epigenetic reconfiguration, and dysregulation of inflammatory and oxidative stress pathways [18]. Perturbations in myocardial fatty acid oxidation, glucose metabolism, and mitochondrial homeostasis contribute to metabolic inflexibility and energetic deficits central to DCM pathogenesis [19]. Normally, the heart exhibits metabolic plasticity by dynamically adjusting its use of substrates such as fatty acids, glucose, lactate, ketone bodies, and amino acids to meet fluctuating adenosine triphosphate (ATP) demands. Under diabetic stress, however, this flexibility is compromised, leading to maladaptive metabolic remodeling that promotes structural and functional deterioration of the myocardium [20, 21].

The gut microbiota has recently emerged as a key modulator of host metabolic homeostasis, acting as a metabolic organ that communicates bidirectionally with distant tissues through the gut–heart axis [22]. This complex microbial ecosystem influences myocardial metabolism and inflammatory tone via the production of bioactive metabolites, thereby contributing to cardiac remodeling in DCM. The human gut harbors approximately 10^{14} microorganisms, whose collective genomic output and metabolic activity profoundly affect host physiology [23]. Disruption of microbial composition—dysbiosis—is closely linked to metabolic disorders, including type 2 diabetes and heart failure [24–30]. Although individual studies have explored the contributions of gut microbiota to these diseases, a comprehensive synthesis of how gut-derived metabolites mediate metabolic reprogramming in DCM remains lacking.

In this review, literature was systematically retrieved from PubMed and Web of Science databases using combinations of keywords such as “diabetic cardiomyopathy”, “gut microbiota”, “microbial metabolites”, “metabolic reprogramming”, “prebiotics”, “epigenetic dysregulation”, and “cardiac metabolism”. Articles published in English up to April 2025 were considered. Inclusion criteria encompassed original research articles and reviews that addressed mechanistic insights, therapeutic interventions, or clinical associations between gut microbiota and DCM. Studies unrelated to DCM, non-peer-reviewed sources, and those without microbiota-related content were excluded. This review delineates the mechanistic pathways by which the gut microbiota contributes to metabolic reprogramming in diabetic cardiomyopathy, including energy metabolism alterations, epigenetic modifications, and inflammatory signaling. We further explore the therapeutic implications of modulating gut microbiota composition and function, evaluate preclinical and translational interventions, and identify current limitations and future directions. By integrating insights from cardiovascular metabolism, microbiome science, and translational research, this review seeks to provide a conceptual framework for precision therapy development for DCM.

2 | Metabolic Reprogramming in DCM

2.1 | Energy Metabolic Reprogramming in DCM

The heart is an energetically demanding organ, primarily reliant on mitochondrial oxidative phosphorylation for ATP production. Under physiological conditions, mitochondria occupy

more than 30% of cardiomyocyte volume [31] and supply approximately 95% of myocardial ATP, with glycolysis accounting for the remainder [32]. In the healthy adult heart, fatty acids contribute 40 to 70% of ATP production, while glucose accounts for 20 to 30%; minor contributions arise from ketone bodies, lactate, and branched-chain amino acids (BCAAs) [33]. This metabolic flexibility allows the myocardium to dynamically adapt to energetic needs. However, in DCM, this flexibility is impaired, leading to maladaptive metabolic remodeling.

A complex and heterogeneous metabolic phenotype characterizes DCM. Evidence from preclinical models and patient studies indicates that metabolic reprogramming is central to DCM pathogenesis [34]. While failing hearts often demonstrate reduced fatty acid oxidation with a compensatory increase in glucose utilization [35], DCM displays an atypical pattern: enhanced fatty acid uptake accompanied by impaired glucose oxidation [36]. This substrate inflexibility, driven by the diabetic milieu, promotes inefficient ATP generation and lipid accumulation, exacerbating myocardial dysfunction. Figure 1 illustrates key differences in substrate handling between the healthy heart and DCM myocardium.

2.1.1 | Glucose Metabolism Reprogramming in DCM

Hyperglycemia-associated alterations in myocardial glucose metabolism are primarily driven by insulin resistance (IR) and glucotoxicity [37]. IR impairs insulin-mediated translocation of glucose transporter 4 (GLUT4) to the cardiomyocyte membrane, thereby reducing glucose uptake and increasing reliance on circulating free fatty acids [38]. This shift promotes mitochondrial overload, oxidative stress, and energetic inefficiency. Furthermore, IR redirects glucose flux into alternative pathways—including the hexosamine biosynthetic pathway, protein kinase C (PKC) activation, advanced glycation end-product (AGE) formation, and the polyol pathway—all of which impair mitochondrial function, calcium handling, and contractility [39, 40]. At the molecular level, AGEs interact with their receptor (RAGE) on cardiomyocytes, activating downstream the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) [41], phosphoinositide-3 kinase (PI3K)/Akt [42], and mitogen-activated protein kinase (MAPK)/nuclear factor kappa-B (NF-κB) [43] signaling cascades. These pathways converge to drive oxidative stress, proinflammatory gene expression, and profibrotic remodeling, ultimately contributing to myocardial stiffening and diastolic dysfunction [44].

2.1.2 | Other Energy Substrate Metabolism in DCM

Lipotoxicity is a hallmark of DCM, arising from increased fatty acid uptake and impaired mitochondrial oxidation. In diabetic hearts, overexpression of the fatty acid transporter cluster of differentiation 36 (CD36) enhances myocardial uptake of long-chain fatty acids (LCFAs), leading to ectopic triglyceride accumulation and metabolic stress [45, 46]. Aberrant subcellular

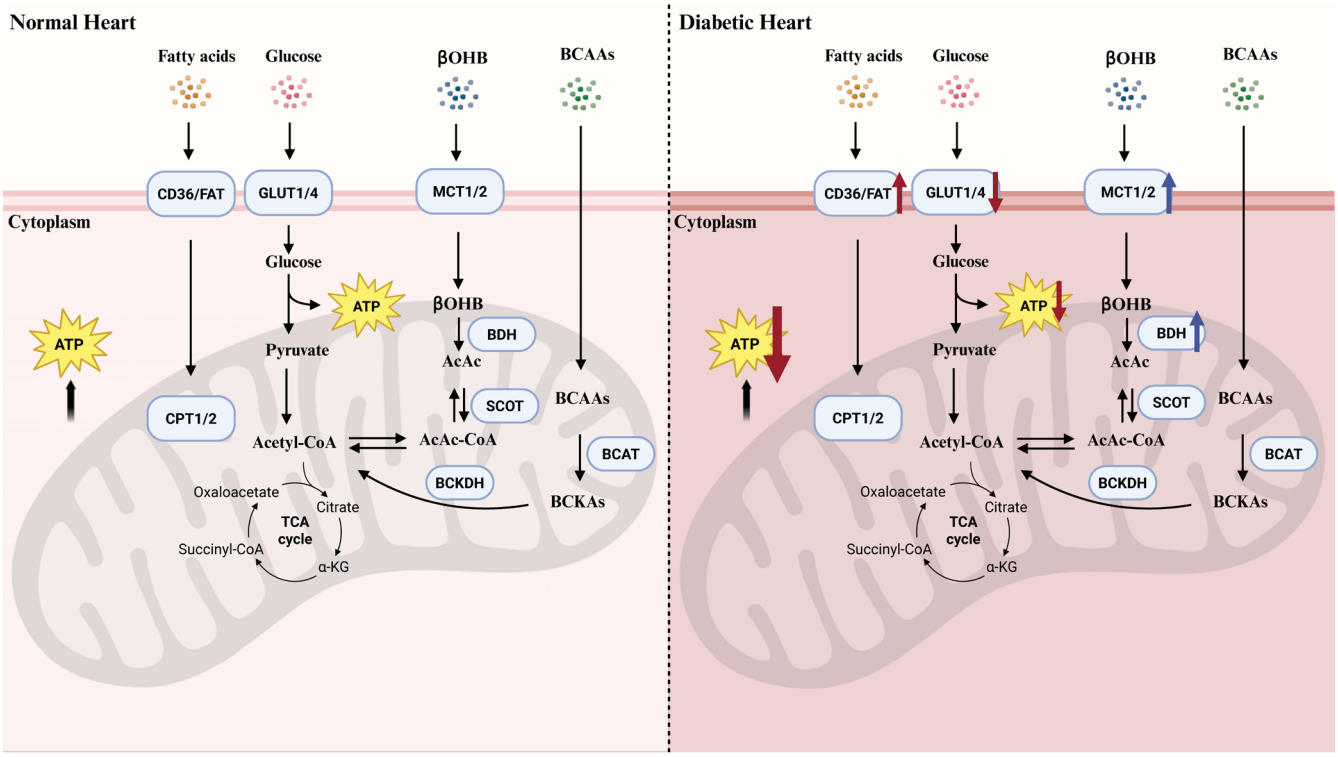

FIGURE 1 | Normal cardiac energy metabolism vs. metabolic reprogramming in diabetic cardiomyopathy. α-KG, α-ketoglutaric acid; β-OHB, β-hydroxybutyrate; ATP, adenosine 5′-triphosphate; BCAAs, branched-chain amino acids; BCAT, branched-chain amino acids transferase; BCKDH, branched-chain ketoacid dehydrogenase; BDH, 3-hydroxybutyrate dehydrogenase; CD36, cluster of differentiation 36; CPT, carnitine O-palmitoyltransferase; FAT, fatty acid transporter; GLUT, glucose transporter; MCT, monocarboxylate transporter; SCOT, succinyl CoA, 3-oxoacid CoA transferase; TCA cycle, tricarboxylic acid cycle.

distribution of CD36—particularly its translocation to the sarcolemmal membrane—exacerbates lipid overload and contributes to cardiac dysfunction [47]. Paradoxically, CD36 deletion impairs fatty acid metabolism and worsens energetic deficits in DCM models, underscoring the delicate balance between substrate supply and utilization [48, 49]. Excess intracellular lipids generate toxic intermediates, such as diacylglycerol, acylcarnitines, and ceramides, which impair contractility and promote apoptosis [50].

In states of insulin deficiency, accelerated lipolysis leads to elevated circulating ketone bodies. Although ketone oxidation is upregulated in failing hearts, DCM presents a paradox: increased systemic ketogenesis with impaired myocardial ketone utilization. In DCM models, key ketolytic enzymes such as 3-hydroxybutyrate dehydrogenase 1 (BDH1) and Succinyl CoA: 3-oxoacid CoA transferase (SCOT) are downregulated despite elevated expression of hydroxymethylglutaryl-CoA synthase 2, a ketogenesis driver [12]. This suggests a supply and oxidation capacity mismatch, contributing to metabolic inefficiency [51]. The clinical relevance of ketone metabolism in diabetic hearts remains controversial, with some studies suggesting compensatory utilization and others reporting impaired oxidation [52].

Elevated BCAA levels have been linked to insulin resistance and heightened cardiometabolic risk [53]. In DCM, impaired BCAA catabolism—due to reduced activity of branched-chain α-ketoacid dehydrogenase (BCKDH)—results in myocardial BCAA accumulation [54, 55]. Epigenetic regulation further compounds this defect; hyperglycemia activates the TGF-β/Smad axis, suppressing transcription of BCAA-catabolizing enzymes (e.g., BCAT2, PP2Cm) through promoter deacetylation [56]. Accumulated BCAAs perturb glucose and lipid metabolism and function as signaling molecules that exacerbate cardiac remodeling and metabolic stress.

2.2 | Epigenetic Regulation in DCM

Epigenetic dysregulation plays a central role in the development of DCM by altering gene expression patterns without modifying the underlying DNA sequence. Key epigenetic mechanisms include histone modifications, DNA methylation, and noncoding RNA regulation. Hyperglycemia-induced upregulation of histone deacetylase 3 (HDAC3) promotes fibrotic gene expression, including TGF-β and Col1a1, while HDAC inhibition reverses this profibrotic remodeling [57]. DNA methylation changes are also implicated; in DCM patients, hypomethylation of the Kelch-like ECH-associated protein 1 (KEAP1) promoter enhances KEAP1 expression, destabilizing nuclear factor E2-related factor 2 (NRF2) and impairing antioxidant responses [58].

MicroRNAs (miRNAs) are central regulators of fibrosis, apoptosis, and hypertrophy in DCM [59]. For instance, miR-21 enhances myocardial fibrosis via SPRY1 suppression and ERK–MAPK pathway activation [60]; miR-27a-3p inhibition attenuates perivascular fibrosis by restoring NRF2 and blocking endothelial–mesenchymal transition [61]; miR-208a, upregulated in both diabetic mice and human DCM hearts, induces hypertrophy via β-MHC upregulation, and its blockade ameliorates cardiac remodeling [62]. miR-30c exerts dual effects by targeting PGC-1β and modulating PPARα signaling, reducing apoptosis while improving metabolic flexibility and cardiac function [63].

Long noncoding RNAs (lncRNAs) also contribute significantly. MALAT1 promotes cardiomyocyte apoptosis and dysfunction through the EZH2/miR-22/ABCA1 axis [64]. These findings highlight the regulatory potential of both miRNAs and lncRNAs in the metabolic and fibrotic remodeling of DCM.

2.3 | Inflammation and Oxidative Stress in DCM

Chronic low-grade inflammation and oxidative stress are pivotal drivers of DCM progression. Hyperglycemia activates fibroblast growth factor receptor 1 (FGFR1) via Toll-like receptor 4 (TLR4), triggering MAPK-mediated NF-κB signaling and promoting inflammatory cytokine release, fibrosis, and hypertrophy [65]. Concurrently, excessive lipid uptake impairs mitochondrial dynamics and amplifies reactive oxygen species (ROS) production, which alters post-translational modifications of key mitochondrial regulators such as optic atrophy 1 (OPA1) and dynamin-related protein 1 (DRP1) [66]. These disruptions exacerbate mitochondrial fragmentation and bioenergetic failure. Inflammatory cytokines—particularly tumor necrosis factor-α (TNF-α)—stimulate ROS via NADPH oxidase 2 (NOX2), while ROS perpetuate inflammation through NF-κB activation, establishing a feed-forward loop of oxidative-inflammatory injury [67].

3 | Gut Microbiota and DCM

3.1 | Overview of Gut Microbiota

The human gastrointestinal tract harbors a highly diverse and dynamic ecosystem of microorganisms—collectively termed the gut microbiota—comprising bacteria, archaea, eukaryotes, viruses, and parasites [68]. This microbial consortium possesses a gene repertoire that exceeds the human genome by over 150-fold, enabling the production of a wide array of metabolites and bioactive molecules [69]. The gut microbiota is dominated by five phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Fusobacteria*, with *Firmicutes* and *Bacteroidetes* together accounting for approximately 90% of the total bacterial population [70, 71]. Shifts in the *Firmicutes*-to-*Bacteroidetes* ratio have been associated with various physiological and pathological states, including metabolic disorders [72]. The gut microbiota composition is influenced by both intrinsic factors (e.g., host genetics, immune status) and extrinsic factors (e.g., diet, medications) [73]. For instance, diets rich in fat and protein often exhibit a *Bacteroides*-dominant enterotype, while fiber-rich diets favor *Prevotella* prevalence [74].

The gut microbiota plays an integral role in host metabolic regulation through its enzymatic, immunomodulatory, and signaling functions, warranting its designation as a metabolic organ [75]. Recent advances in metagenomics, metabolomics, and high-throughput sequencing technologies have shifted the scientific focus from mere compositional profiling to functional microbiome characterization [76]. Dysbiosis—defined as a loss of microbial diversity and an increase in pro-inflammatory taxa—has

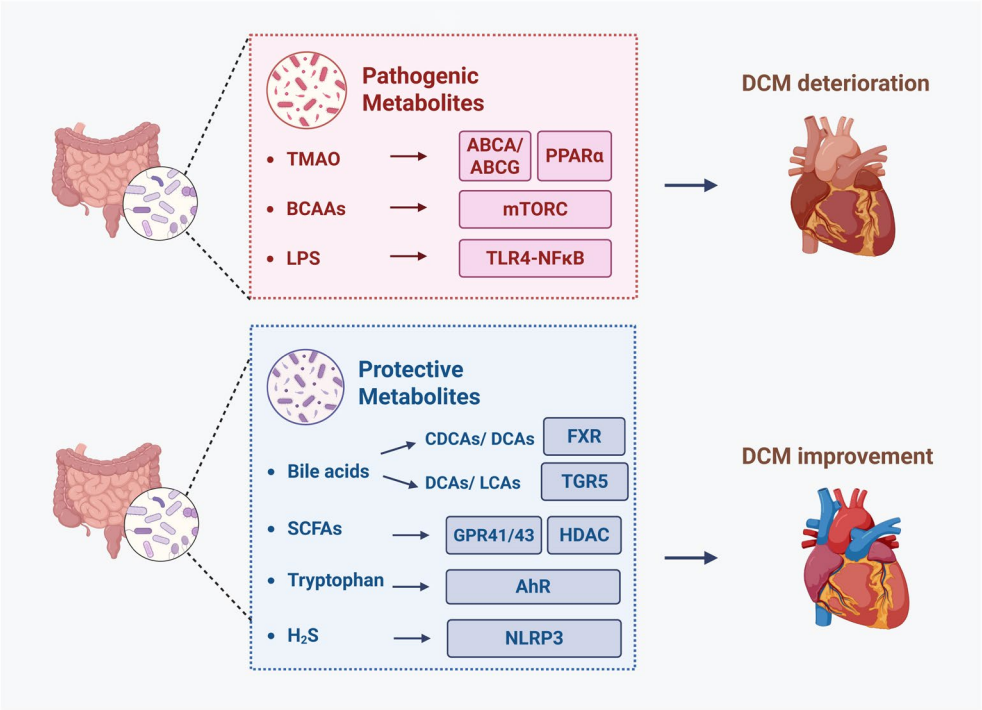

FIGURE 2 | Gut microbiota metabolites and the associated metabolic signaling pathways in DCM. ABCA: ATP-binding cassette transporter A. ABCA, ATP-binding cassette transporter A; ABCG, ATP-binding cassette transporter G; AhR, Aryl hydrocarbon receptor; CDCAs, chenicoxycholic acids; DCAs, deoxycholic acids; FXR, farnesoid X receptor; GPR41/43, G-protein-coupled receptor 41/43; HDAC, histone deacetylase; LCAs, lithocholic acids; mTOR, Mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; PPARα, peroxisome proliferator-activated receptor alpha; TGR5, Takeda G protein-coupled receptor 5; TLR4, toll-like receptor 4.

been implicated in the pathogenesis of multiple chronic diseases, including type 2 diabetes, non-alcoholic fatty liver disease, autoimmune disorders, and cardiovascular conditions [28, 77–89]. Given its capacity to influence systemic metabolism, immune signaling, and host-microbe co-metabolism, gut microbiota has emerged as a promising therapeutic target in DCM.

3.2 | Gut Microbiota-Derived Metabolites in DCM

The pathogenic potential of the gut microbiota in DCM is largely mediated by its metabolites, which exert diverse effects depending on host metabolic state, dietary intake, and organ-specific sensitivity [90]. Key microbial metabolites—such as short-chain fatty acids (SCFAs), trimethylamine N-oxide (TMAO), bile acids (BAs), lipopolysaccharides (LPS), tryptophan catabolites, and hydrogen sulfide (H_2S)—modulate host pathways involved in inflammation, oxidative stress, mitochondrial function, and fibrotic remodeling. Figure 2 illustrates these metabolites and their corresponding signaling cascades relevant to DCM.

3.2.1 | Trimethylamine N-Oxide (TMAO)

TMAO is a gut microbiota-derived metabolite produced through microbial metabolism of dietary precursors such as choline, betaine, and carnitine. These substrates are converted into trimethylamine (TMA) in the colon and oxidized to TMAO in the liver via flavin-containing monooxygenases [91]. Elevated TMAO levels have been linked to a spectrum of cardiometabolic diseases, including atherosclerosis [92], hypertension [93], chronic kidney disease [94–98], and diabetes [99, 100]. In DCM, TMAO exacerbates cardiac dysfunction through mechanisms that include myocardial fibrosis [101], impaired contractility [102], and enhanced thrombogenesis [103]. It also impairs glucose metabolism by downregulating insulin signaling and reducing hepatic glycogen storage [104]. Additionally, TMAO upregulates hydroxymethylglutaryl-coenzyme A reductase and downregulates cholesterol efflux transporters ABCA1 and ATP-binding cassette transporter G1 (ABCG1), thereby disturbing lipid homeostasis [104]. Despite accumulating evidence, the precise contribution of TMAO to DCM pathogenesis warrants further mechanistic investigation.

3.2.2 | Bile Acids

Bile acids (BAs) are the primary products of cholesterol metabolism in the liver, and the gut microbiota plays a crucial role in their synthesis. The process of converting cholesterol into primary BAs such as cholic acid (CA) and chenodeoxycholic acid (CDCA) occurs via both the classical and alternative pathways, with CYP7A1 catalyzing the former and CYP27A1 the latter. The gut microbiota modifies primary BAs through deconjugation and dehydroxylation, leading to the formation of secondary BAs such as deoxycholic acid (DCA) and lithocholic acid (LCA).

Beyond their digestive roles, BAs act as signaling molecules that activate Farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) [105, 106]. FXR is primarily activated

by CDCA and DCA, while TGR5 is more potently activated by LCA and DCA [107]. Activation of FXR and TGR5 modulates glucose and lipid metabolism, enhances insulin sensitivity, and regulates energy expenditure [108–110]. In the context of DCM, these pathways regulate gluconeogenesis, promote glycogen synthesis, and reduce triglyceride accumulation [111, 112]. Key signaling axes include BA-FXR-fibroblast growth factor (FGF)15/19 and BA-TGR5-glucagon-like peptide 1 (GLP-1), which mediate cAMP and GLP-1 pathways [113–115]. Thus, modulation of BA signaling presents a promising therapeutic strategy for DCM.

3.2.3 | Short-Chain Fatty Acids (SCFAs)

SCFAs—primarily acetate, propionate, and butyrate—are produced through bacterial fermentation of dietary fibers and constitute a major component of the gut metabolome [116–118]. These molecules are absorbed by colonocytes and contribute to systemic energy metabolism, including in the myocardium. SCFAs act via G protein-coupled receptors (e.g., GPR41/43) and inhibit histone deacetylases, thereby modulating gene expression, immune function, and metabolic homeostasis [119, 120]. For instance, SCFA activation of GPR43 enhances GLP-1 secretion, while propionate-induced GPR41 signaling increases leptin production [121, 122]. SCFAs also exhibit anti-inflammatory effects by suppressing ROS production and promoting neutrophil apoptosis [123–127], suggesting cardioprotective roles in DCM via modulation of immune-metabolic signaling.

3.2.4 | Lipopolysaccharides (LPS)

LPS, integral components of Gram-negative bacterial outer membranes, activate Toll-like receptor 4 (TLR4) signaling through myeloid differentiation primary response protein 88 (MyD88)-dependent and TIR-domain-containing adaptor inducing interferon-β (TRIF)-dependent pathways [128, 129]. These cascades induce NF-κB activation and cytokine production, contributing to chronic inflammation and metabolic endotoxemia. Elevated circulating LPS levels in diabetes correlate with endothelial dysfunction and oxidative stress via VEGF upregulation [130]. In murine models, LPS-driven TLR4 activation impairs myocardial contractility and promotes cardiac inflammation [131]. However, certain commensal-derived LPS, particularly from Bacteroides species, may exhibit immunomodulatory effects by antagonizing pro-inflammatory TLR4 signaling [132]. These dual roles highlight the nuanced impact of LPS on host homeostasis and DCM.

3.2.5 | Tryptophan Metabolites

Tryptophan metabolism involves both host (kynurenine, serotonin pathways) and microbial (indole derivatives) routes, generating bioactive compounds that influence immunity, metabolism, and gut barrier integrity [133–138]. Kynurenine pathway metabolites, such as kynurenic acid, activate GPR35 and promote adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation, thereby reducing inflammation and insulin resistance [136]. Indole-3-propionic acid, a microbial metabolite, enhances nicotinamide adenine dinucleotide (NAD^+) salvage and protects against diastolic dysfunction in HFpEF [139]. These findings underscore the relevance of tryptophan-derived metabolites in modulating cardiometabolic signaling and offer potential therapeutic targets for DCM.

3.2.6 | Hydrogen Sulfide (H_2S)

H_2S, produced by gut microbial metabolism of cysteine and sulfate-reducing bacteria (e.g., *Desulfovibrio*) [140–142], is now recognized as a gaseous signaling molecule with cardioprotective properties [143–145]. In DCM models, H_2S supplementation alleviates mitochondrial dysfunction, reduces ROS, and suppresses NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome activation [146]. Additionally, H_2S preserves RAR-related orphan receptor α (RORα) expression via the RORα–STAT3 axis and improves GLP-1 signaling through the inositol-requiring enzyme 1α (IRE1α) pathway [147, 148]. These findings highlight H_2S as a microbiota-derived mediator with therapeutic potential in DCM.

Although several animal studies have clarified the gut microbiota and its metabolic products in diabetic cardiomyopathy, substantial human-specific data gaps exist. Inter-species variation in microbial identity, metabolite composition, and gut-microbe interaction preclude a direct extrapolation of preclinical data to humans. In addition, the majority of human studies so far are cross-sectional in nature and have sparse longitudinal datasets that provide associations between the dynamic properties of the microbiome and the onset or advancement of DCM. Interindividual differences in diet, geography, and heredity in human populations add complexity to the identification of persistent microbial markers. These constraints highlight the immediate need for extensive-scale, longitudinal, and multi-ethnic human cohorts using standardized microbiome profiling and integrative clinical phenotyping to more accurately define aetiologic associations and therapeutic targets on the human gut–heart axis.

4 | Gut Microbiota Modulates DCM Through Metabolic Reprogramming

While the gut microbiota typically maintains a dynamic equilibrium within the host, external stressors—including dietary imbalance, inflammation, and oxidative stress—can disturb this balance, leading to dysbiosis. Dysbiosis disrupts metabolic homeostasis by altering microbial community structure and the bioavailability of microbial metabolites. Accumulating evidence implicates gut microbial dysbiosis as a fundamental mediator in the pathogenesis of DCM. For example, data from the Framingham Heart Study (FHS) cohort revealed significant associations between specific bacterial families—such as *Ruminococcaceae*, *Clostridiales*, and *Lachnospiraceae*—and the incidence of type 2 diabetes and cardiovascular disease (CVD) [149]. *Lachnospiraceae*, in particular, are key butyrate producers, and the reduced abundance of this

group may contribute to impaired metabolic regulation [148]. Moreover, DCM rat models have demonstrated significant depletion of beneficial genera, including *Bifidobacterium* and *Lactobacillus*, which are known to influence host energy metabolism via PPARγ signaling [150]. These findings highlight the centrality of microbial composition and function in modulating DCM progression.

4.1 | Gut Microbiota Remodels Glucose Metabolism in DCM

The gut microbiota exerts significant regulatory control over host glucose metabolism, directly affecting DCM. A meta-analysis revealed that circulating TMAO concentrations in heart failure patients show substantial elevation compared to healthy controls [151]. This result was validated by Huang et al., who used high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS) to quantify serum TMAO levels in DCM mice, showing that TMAO exacerbates glucose intolerance and cardiac fibrosis by activating protein kinase R-like endoplasmic reticulum kinase (PERK)-mediated transcription of forkhead box protein O1 (FOXO1), a pro-apoptotic and pro-fibrotic transcription factor implicated in cardiac remodeling [152]. In parallel, GLP-1 and its receptor signaling axis—which are integral to glucose regulation—are influenced by gut microbial composition. For instance, *Prevotella copri* modulates GLP-1 secretion through cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) activation in response to microbial metabolites [153], while microbiota-derived L-tryptophan has been shown to upregulate GLP-1-related gene expression (*Gcg* and *Pcsk1*) [154]. Additionally, in diabetic mouse models, GLP-1 receptor agonists (GLP-1RAs) improve myocardial glucose oxidation and diastolic function via pyruvate dehydrogenase activation [155]. These data underscore the capacity of microbial metabolites to regulate glycemic control and cardiac function in DCM.

4.2 | Gut Microbiota Remodels Other Energy Substrate Metabolism in DCM

The gut microbiota also modulates lipid, ketone, and amino acid metabolism, influencing cardiac energy substrate utilization in DCM. Activation of the TGR5 receptor by microbial bile acids has been shown to suppress CD36-mediated fatty acid uptake, mitigating lipotoxicity and myocardial dysfunction in diabetic mice [156]. Conversely, reduced circulating short-chain fatty acid (SCFA) levels—particularly butyrate—have been observed in DCM patients, correlating with dysregulated lipid profiles [157, 158]. SCFAs also positively regulate fasting GLP-1 and inhibit adipocyte lipolysis, suggesting a role in systemic lipid homeostasis. In murine models, polysaccharide supplementation elevates plasma L-arginine and activates the NO/PPARα/carnitine O-palmitoyltransferase (CPT) 1A axis, improving lipid metabolism and mitochondrial fatty acid oxidation [159].

Additionally, ketone body and BCAA metabolism in DCM are increasingly recognized as microbiota-sensitive processes. The Microbe4U trial demonstrated that oral administration of *Akkermansia muciniphila* shifts systemic metabolism toward increased β-oxidation and ketogenesis in individuals with metabolic syndrome [160]. Impaired microbial degradation of BCAAs has also been linked to elevated myocardial BCAA concentrations, contributing to insulin resistance and oxidative stress in Type 1 Diabetes Mellitus (T1DM) mice [161]. Importantly, the *porA* gene in *Parabacteroides merdae* has been identified as a key genetic determinant of microbial BCAA catabolism, with knockout models displaying impaired BCAA breakdown and heightened susceptibility to cardiometabolic disease [162]. These findings emphasize the gut microbiota's influence on cardiac substrate metabolism and its potential as a therapeutic target in DCM.

4.3 | Gut Microbiota Regulates Epigenetic Pathways in DCM

Emerging research suggests that the gut microbiota influences host epigenetic programming via metabolites such as SCFAs and TMAO. SCFAs—including butyrate—act as histone deacetylase (HDAC) inhibitors, enhancing histone acetylation and promoting the expression of antifibrotic and antioxidant genes [163]. In diabetic models, butyrate-mediated HDAC inhibition upregulates cardioprotective genes such as Inpp5f and enhances GLUT1/GLUT4 expression, promoting angiogenesis and reducing oxidative stress and apoptosis [164, 165]. Furthermore, SCFA levels are inversely correlated with DNA methylation at the HIF3A promoter in DCM patients, suggesting a role for microbial metabolites in regulating hypoxia-related signaling [157]. On a post-transcriptional level, TMAO has modulated microRNA expression—including miR-21-5p and miR-30c—both implicated in insulin resistance and fibrotic remodeling in DCM [63, 166, 167]. Collectively, these findings highlight gut microbiota-mediated epigenetic remodeling as a critical node in the pathophysiology of DCM.

4.4 | Gut Microbiota Modulates Inflammation and Oxidative Stress in DCM

Chronic low-grade inflammation and oxidative stress are central to the pathogenesis of DCM, and the gut microbiota modulates these pathways through pro-inflammatory and anti-inflammatory mechanisms. LPS from gut dysbiosis activates the ERK/Egr-1 axis, promoting cardiac inflammation and injury [168], while TMAO has been shown to induce ferroptosis and mitochondrial dysfunction in diabetic hearts [169]. Excess BCAA levels impair hepatic FGF21 production and promote the L-type amino acid transporter 1 (LAT1) expression in the myocardium via Zbtb7c, leading to oxidative damage through mTOR activation [161].

Conversely, several microbiota-derived interventions confer anti-inflammatory and antioxidative effects. Heat-inactivated *Lactobacillus reuteri* downregulates TLR4 signaling, attenuating myocardial inflammation in diabetic rats [170]. Bile acid signaling through TGR5-cAMP-PKA suppresses NLRP3 inflammasome activation, mitigating cardiac inflammation [171]. Similarly, hydrogen sulfide donors such as NaHS inhibit the TLR4/NF-κB axis, reducing cardiomyocyte injury under

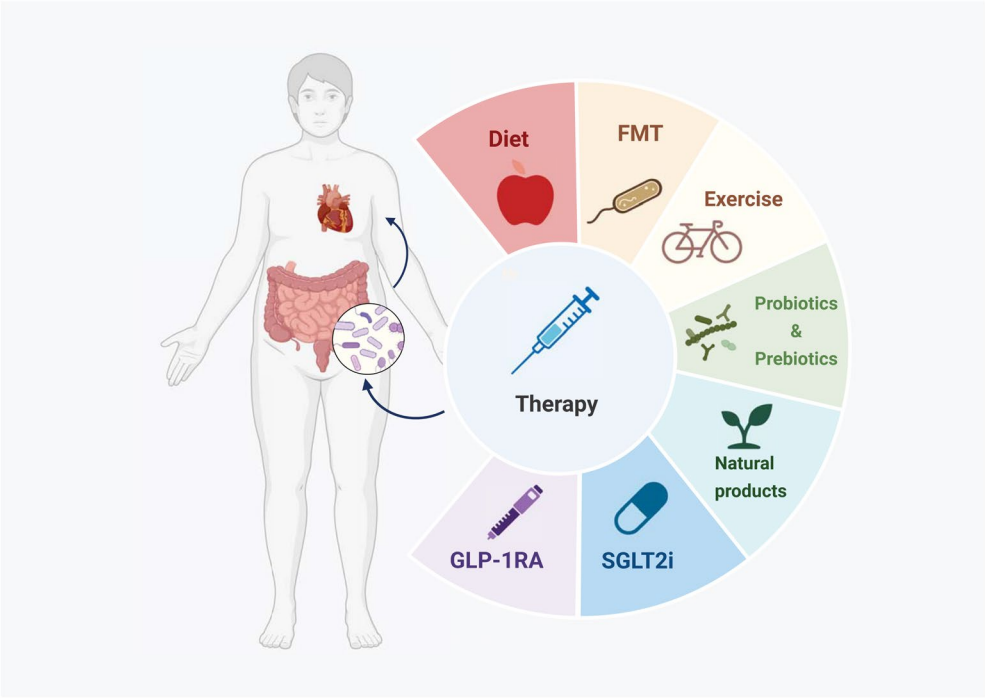

FIGURE 3 | Gut microbiota-based therapies for diabetic cardiomyopathy. FMT, fecal microbiota transplantation; GLP1-RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

hyperglycemic conditions [172]. These dualistic actions of microbial metabolites reinforce the gut microbiota's pivotal role in regulating oxidative and inflammatory cascades in DCM, offering opportunities for precision-targeted therapies.

5 | Gut Microbiota-Based Therapies for Diabetic Cardiomyopathy

Despite extensive research into the development and pathophysiology of DCM, targeted pharmacological therapies remain unavailable. Recent findings suggest that certain conventional treatments may exert previously unrecognized therapeutic effects through modulation of the gut microbiota. As our understanding of the gut–heart axis evolves, gut microbiota-targeted interventions are emerging as promising strategies for metabolic reprogramming, inflammation reduction, and cardiac function restoration in DCM. Figure 3 depicts an overview of these interventions.

5.1 | Diet

Dietary composition is critical in shaping gut microbiota diversity and metabolic output. The ketogenic diet (KD), characterized by high fat and low carbohydrate intake, has demonstrated cardioprotective effects in animal models of DCM by improving mitochondrial dynamics, reducing myocardial apoptosis, and promoting metabolic flexibility [173–175]. In contrast, Western dietary patterns rich in saturated fats and simple sugars have been shown to promote dysbiosis, systemic inflammation, and metabolic endotoxemia, all contributing to DCM progression [176, 177]. Controlled studies in both human and animal models indicate that dietary modulation directly impacts gut microbial composition, independent of host genetic background [178].

5.2 | Fecal Microbiota Transplantation (FMT)

FMT involves the transfer of a healthy donor's fecal microbiota to a recipient to restore gut microbial balance and function [179]. Preclinical studies suggest that FMT may reverse DCM-related pathologies by modulating inflammation and improving gut barrier integrity. For example, fecal material from myricetin- or resveratrol-treated diabetic mice has been shown to confer cardioprotective effects when transplanted into microbiota-depleted or untreated DCM mice, reducing myocardial fibrosis and inflammatory signaling [180, 181]. While promising, FMT faces clinical barriers, including donor screening, infection risk, and standardization.

Although FMT holds therapeutic potential, its translation to the clinic is hindered by major regulatory hurdles. These include the absence of standard donor screening protocols, heterogeneity in the composition of the microbiota, and fears of long-term safety and risk of infection. Regulatory bodies such as the FDA now define FMT as an investigational product subject to rigorous scrutiny and clinical trial supplementation. In addition to this, ethical and practical considerations such as donor–recipient matching and quality assurance—all add complexity to broader clinic adoption. Thus, although FMT as a therapeutic approach holds interest, its inclusion in the clinic requires harmonization of regulatory systems and intensive safety tracking.

5.3 | Exercise

Emerging evidence suggests that physical exercise exerts beneficial effects on DCM not only through classical pathways such as improved insulin sensitivity and reduced inflammation, but also by reshaping the gut microbiota. Chronic exercise alters the composition of gut microbial communities, promoting beneficial taxa such as *Firmicutes* and SCFA-producing bacteria, while reducing pro-inflammatory strains like *Bacteroides/Prevotella* spp. [182, 183]. These microbial changes enhance gut barrier integrity, lower systemic inflammation, and improve insulin sensitivity, which is relevant to DCM pathophysiology. Moreover, FMT from exercised donors to diabetic mice improved vascular function, glucose regulation, and reduced oxidative stress, suggesting that exercise-induced microbiota changes can directly impact DCM through a gut–vascular axis [184]. These findings position the gut microbiota as a mediator of exercise benefits and a potential target for DCM intervention.

5.4 | Probiotics and Prebiotics

Probiotics are microorganisms enriched in healthy individuals (compared with those altered health states), considered beneficial, and associated with health benefits when administered to humans [185]. Common probiotics, including *Bifidobacterium*, *Lactococcus*, and *Lactobacillus* strains, exert beneficial effects by modulating gut microbial composition and reducing systemic inflammation [186]. In rat models, probiotic administration demonstrated a capacity to decrease myocardial hypertrophy and heart failure after myocardial infarction [187]. A research study evaluated the impact of a probiotic supplement comprising *Bifidobacterium bifidum*, *Lactobacillus casei*, and *Lactobacillus acidophilus* (each administered at 2×10^9 CFU/day) among diabetic individuals with cardiovascular disease. Following a 12-week period, participants demonstrated enhanced glucose and lipid metabolism and decreased levels of oxidative stress biomarkers [188].

In the most recent position statement issued by the Global Prebiotic Association, prebiotics—such as inulin, galactooligosaccharides, and resistant starch—serve as fermentable substrates for commensal bacteria, increasing SCFA production and promoting anti-inflammatory effects [189, 190]. Despite their potential, host-specific responses and risks of microbial imbalance highlight the need for precision-guided probiotic and prebiotic interventions, supported by multi-omics technologies and large-scale clinical validation.

5.5 | Natural Products

Bioactive natural compounds, including polyphenols (e.g., resveratrol, quercetin) and alkaloids (e.g., berberine), have shown efficacy in modulating gut microbiota and improving DCM phenotypes in preclinical models [191–196]. Resveratrol enhances mitochondrial function, reduces lipid accumulation, and attenuates fibrosis while shifting gut microbial composition toward SCFA-producing taxa [197]. Quercetin, the most abundant flavonoid, possesses strong antioxidant activity [198]. It reduces the abundance of Proteobacteria, Bacteroides, Escherichia-Shigella, and *Escherichia coli*, potentially serving as a mechanism for alleviating IR in db/db mice [199]. Berberine improves glucose and lipid metabolism, suppresses apoptosis, and preserves mitochondrial homeostasis via PI3K/AKT/GSK3β signaling while enriching beneficial bacterial genera [200–203]. These compounds may also undergo microbial biotransformation, yielding active metabolites that reinforce their therapeutic potential.

5.6 | Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i have emerged as first-line cardiometabolic therapies, reducing heart failure risk and improving cardiovascular outcomes in patients with or without diabetes [204]. In DCM models, SGLT2i enhance myocardial ketone body utilization, activate oxidative phosphorylation enzymes, and improve ATP synthesis, collectively preserving mitochondrial integrity and reducing oxidative stress [12]. While the cardioprotective mechanisms of SGLT2i are not fully elucidated, evidence suggests a potential microbiota-mediated component [205, 206]. For instance, empagliflozin increases the abundance of SCFA-producing bacteria (e.g., *Roseburia*, *Faecalibacterium*) and reduces pro-inflammatory taxa (e.g., *Escherichia-Shigella*) [207]. A bidirectional Mendelian randomization study suggests that SGLT2i may influence metabolic heart disease through gut microbiome metabolites such as choline [208]. Additionally, evidence shows that the combination of dapagliflozin with probiotics and prebiotics alleviates DCM by activating PPARγ [169].

Although reviews have described the relationship between SGLT2i and gut microbiota [205], direct evidence of SGLT2i intervening in DCM through gut microbiota modulation remains limited. Further in-depth research needs exploring in the future to fill the existing knowledge gap and clarify the specific mechanism by which SGLT2i affects metabolic heart disease.

5.7 | GLP-1 Receptor Agonists (GLP-1 RA)

GLP-1 RAs are incretin-based therapies with established glucose-lowering and cardioprotective effects [209, 210]. These agents may benefit through modulation of gut microbiota, as evidenced by increased abundance of SCFA-producing taxa and improved intestinal barrier function in diabetic rodent models treated with liraglutide [211]. Tryptophan-derived metabolites also enhance GLP-1 synthesis and secretion via upregulation of *Gcg* and *Pcsk1* gene expression [154]. While direct clinical evidence remains limited, these findings suggest that the interplay between GLP-1 RA and gut microbiota contributes to cardiometabolic modulation in DCM.

In summary, an array of microbiota-targeting interventions ranging from dietary modification, microbial transplantation, probiotics/prebiotics, phytochemicals, to glucose-reducing agents has been promising to modulate reprogramming of the metabolism and relieve DCM in both the preclinical and early clinical settings. To enhance record clarity and clinical usability, Table 1 gives a systemic summary of these types of intervention, their respective measures, mechanisms of action, major molecular targets, therapeutic benefits, and references.

TABLE 1 | Evidence for interventions in DCM by regulating host metabolic reprogramming through gut microbiota and its metabolites.

Intervention	Model	Diabetes type	Specific measures	Key targets	Related gut microbiota or metabolites	Potential advantages	Study type	References
Dietary modulation	Male C57BL/6J mice + HFD/HSD	T2DM	High fat/sugar diet	Lipid metabolism	*Bacteroides*, *Lactobacillus* and *Bifidobacterium*	Non-pharmacologic; targets root dietary drivers	Preclinical study	[212]
	Human	T1DM/ T2DM	Mediterranean diet	IR and BCAA metabolism	*Prevotella copri*; SCFAs	Modulates host metabolism	Clinical study	[213]
FMT	Male C57BL/6J mice + HFD/STZ	T2DM	—	TLR4/MyD88 pathway	*Roseburia*, *Faecalibaculum* and *Bifidobacterium*; SCFAs	Holistic modulation of microbiome; potential long-term effects	Preclinical study	[180]
	Male db/db mice	T2DM		BAT activation and WAT browning	*Bacteroides*, *Parabacteroides*, and *Lactobacillus*; bile acids			[181]
Probiotics	Human	T2DM	Probiotic supplementation	PPARγ, GLUT4, oxidative stress biomarkers	*Bifidobacterium bifidum*, *Lactobacillus casei*, and *Lactobacillus acidophilus*	Safe, accessible, enhances host-microbiota synergy	Clinical study	[188]
Prebiotics	Male Wistar rats + HFD/STZ	T2DM	Inulin	Bax/Bcl-2 pathway	*Lactobacillu plantarum*		Preclinical study	[190]
Natural products	Male C57BL/6J mice + HFD	T2DM	Akebia saponin D	PPAR-γ/FABP4	*Alistipes*, *Prevotella* and *Bifidobacterium*	Multi-targeted; derived from traditional medicine; host-microbe synergy	Preclinical study	[214]
	Male C57BL/6J mice + HFD	T2DM	Isoquercetin	AMPK/FGF21 pathway	*Akkermansia* and *Bacteroides*		Preclinical study	[215]
	Male C57BL/6J mice + HFD/STZ	T2DM	Myricetin	TLR4/MyD88 pathway	*Roseburia*, *Faecalibaculum* and *Bifidobacterium*; SCFAs		Preclinical study	[180]
	Male db/db mice	T2DM	Salidroside	Iron metabolism	*Bacteroides* and *Lactobacillus*		Preclinical study	[216]
							Preclinical study	
	Male C57BL/6J mice + HFD	T2DM	Berberine	BCAA metabolism	*Clostridiales* and *Prevotellaceae*		Preclinical study	[217]

(Continues)

TABLE 1 | (Continued)

Intervention	Model	Diabetes type	Specific measures	Key targets	Related gut microbiota or metabolites	Potential advantages	Study type	References
SGLT2 inhibitors	Human	T2DM	Empagliflozin	Ketone body metabolism	*Roseburia*, *Eubacterium*, and *Faecalibacterium*	Established drugs with added microbiome benefits	Clinical study	[207]
	Male Sprague–Dawley rats + STZ	T1DM	Dapagliflozin	PPARγ	*Muribaculaceae*, *Escherichia-Shigella* and *Prevotella_9*		Preclinical study	[169]
GLP-1 RA	Male Sprague–Dawley rats + HFD/STZ	T2DM	Liraglutide, GLP-1 RA agents	GLP-1, SCFA-producing microbiota, tryptophan metabolism	*Bacteroides*, *Lachnospiraceae*, and *Bifidobacterium*; SCFAs	Dual metabolic and cardiovascular benefits; endogenous gut hormone pathway	Preclinical study	[211]

Abbreviations: BAT, brown adipose tissue; BCAAs, branched-chain amino acids; IR, insulin resistance; SCFAs, short-chain fatty acids; WAT, white adipose tissue.

6 | Challenges and Future Directions for Targeting the Gut Microbiota in DCM

DCM, a prevalent cardiovascular complication of diabetes, is characterized by metabolic inflexibility, glucolipotoxicity, inflammation, and myocardial fibrosis, which collectively contribute to progressive cardiac dysfunction and increased morbidity and mortality [37, 218]. Despite growing recognition of gut microbiota as a modifiable determinant of cardiometabolic health, therapeutic strategies targeting the microbiome remain in early development. While preclinical findings are promising, significant challenges must be addressed to translate these insights into effective, personalized clinical interventions.

The current evidence base linking gut microbiota to DCM is predominantly derived from rodent models. However, interspecies differences in microbial ecology limit the translational validity of these findings. The heterogeneity of microbial metabolites, receptor distributions, and organ-specific responses across disease stages underscores the need for high-resolution, longitudinal human studies. Moreover, there is limited understanding of how dynamic changes in the gut microbiome influence epigenetic remodeling and metabolic reprogramming during the progression of DCM. To enhance translational fidelity, future research should prioritize the development of humanized gut microbiota animal models and multi-organ organoid systems, such as heart-gut co-cultures [219].

Individual variability in microbiota composition poses an additional challenge to therapeutic standardization. Inter-individual differences in microbial taxonomy, functional redundancy, and host-microbiota co-metabolism may influence therapeutic index variability and responsiveness to microbiota-targeted therapies. Consequently, precision microbiome profiling and integrating multi-omics datasets, including metagenomics, metabolomics, and epigenomics, are essential for developing stratified therapeutic approaches. Although multi-omics technologies such as metagenomics, metabolomics, transcriptomics, and epigenomics offer unprecedented insights into microbiota-host interactions, several limitations hinder their translational application. A major challenge is the lack of standardization across omics platforms, including variability in sample processing, data acquisition, and bioinformatic pipelines, which reduces reproducibility and cross-study comparability. Moreover, high-throughput omics analyses remain costly and technically demanding, limiting their accessibility for large-scale or longitudinal human studies. Additionally, the resolution of current technologies often falls short in capturing spatial and temporal dynamics of microbiota–host interactions at the tissue and single-cell levels. Addressing these limitations will require coordinated efforts to develop unified protocols, reduce analytical costs, and enhance spatial–temporal resolution through emerging technologies such as spatial transcriptomics and single-cell multi-omics. Furthermore, bidirectional host-microbiota interactions remain underexplored. While most studies focus on microbial modulation of host pathways, the influence of host genetics and immune phenotype on microbial ecology warrants further investigation [220].

Future research directions should integrate systems biology and artificial intelligence (AI) approaches to identify predictive

microbial signatures for DCM risk stratification and therapeutic response monitoring. Standardized microbial sequencing platforms, harmonized metabolomic workflows, and consensus-based data interpretation frameworks will enable reproducible research and cross-cohort validation. Furthermore, incorporating microbiota-targeted strategies into multi-modal interventions, including SGLT2 inhibitors, GLP-1 receptor agonists, and anti-inflammatory therapies, may amplify therapeutic efficacy. Developing microbiota-derived biomarkers and computational models of microbiota–host dynamics could facilitate real-time personalized treatment regimens.

To propel microbiota-targeted approaches to the bedside, multiple priorities for future clinical investigation are proposed. First and foremost, there is a clear need to discover and validate biomarkers from the microbiota—namely certain microbial taxa, metabolites, and gene signatures—that predict the onset and progression of DCM, as well as the response to treatment. These biomarkers would provide early diagnosis as well as enable risk stratification. Second, study designs in the clinic should incorporate stratified patient cohorts to adjust for intersubject variability in the composition of the microbiota, in metabolic and comorbid conditions. Such strategies will maximize the specificity and relevance of microbiota-directed treatments. Third, the incorporation of multi-omics profiling and longitudinal follow-up in studies will reveal dynamic host–microbiota interaction and causal pathways. Finally, the implementation of standardization of clinical protocols for microbiota-directed treatments is required, i.e., screening of the donor for FMT, dosage regimens for probiotic treatments, and regulation. These collective actions will bridge the bench-to-bedside gap to move gut microbiota research to the bedside as effective individualized treatments for DCM.

7 | Discussion

The gut microbiota and its metabolic by-products have emerged as critical regulators of host metabolism, inflammation, and epigenetic remodeling—key processes in the pathogenesis of DCM. Mounting evidence suggests that microbial metabolites, including SCFAs, TMAO, BAs, and tryptophan derivatives, play a role in modulating energy substrate utilization, mitochondrial function, oxidative stress, and fibrotic remodeling in diabetic hearts.

These mechanistic findings provide strong justification for targeting the gut–heart axis as a novel therapeutic avenue in DCM. Indeed, several microbiota-directed interventions—including dietary modification, pre- and pro-biotic supplementation, polyphenol-rich nutraceuticals, and metabolic agents such as SGLT2 inhibitors and GLP-1 receptor agonists—have demonstrated efficacy in reversing or mitigating the pathological features of DCM in preclinical studies. Notably, some of these pharmacological agents may exert cardioprotective effects, at least in part, by modulating the gut microbiota.

However, translating these promising findings into clinical application remains a formidable challenge. Interspecies variation in microbiota composition and host responses, limited human data on dynamic microbiota–host interactions, and technical barriers to omics integration all constrain current progress. Bridging these gaps will require an integrated, multidisciplinary approach that combines biomarker discovery, patient stratification, and standardized interventional protocols.

Ultimately, the successful clinical deployment of microbiota-targeted therapies for DCM hinges on the ability to identify stable, predictive microbial signatures, account for microbiome heterogeneity, and operationalize gut microbiota manipulation within the framework of precision medicine.

8 | Conclusions

The gut microbiota–metabolite axis represents a pivotal regulator of diabetic cardiomyopathy pathophysiology, mediating metabolic reprogramming, inflammation, and myocardial remodeling. Preclinical and early clinical evidence supports its potential as a novel therapeutic target for intervention. However, to fully realize its clinical promise, substantial translational and methodological hurdles must be addressed.

Future studies should emphasize the use of humanized animal models, standardized protocols for microbiota-based therapies, and longitudinal multi-omics profiling to capture causal pathways and therapeutic responses. Precision-microbiome medicine, anchored in robust biomarker discovery and individualized intervention strategies, holds transformative potential to reframe the clinical management of diabetic heart disease.

By targeting the microbiota–host interface, researchers and clinicians may unlock new avenues for disease prevention, risk stratification, and treatment, ultimately improving outcomes for patients with diabetic cardiomyopathy.

Author Contributions

Conceptualization and writing – original draft preparation: Jing-yu Jin. Resources: Xin-yu Yang and Ru Feng. Methodology: Meng-liang Ye. Data curation: Hui Xu and Jing-yue Wang. Visualization: Jia-chun Hu and Jin-yue Lu. Writing – review and editing: Jian-ye Song, Heng-tong Zuo and Yi Zhao. Funding acquisition: Yan Wang and Qian Tong. Supervision: Yan Wang and Qian Tong. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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