Gut microbiota-derived metabolites in cardiovascular disease: Focus on trimethylamine N-oxide, short-chain fatty acids and bile acids (Review)

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Abstract. The gut-heart axis, where microbial metabolites act as key signaling molecules, represents a notable frontier in cardiovascular medicine. An expanding body of evidence has demonstrated that gut microbiota-derived metabolites, particularly trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs) and bile acids (BAs), play divergent roles in the pathogenesis of cardiovascular diseases. While elevated TMAO levels are consistently linked to pro-atherogenic and pro-thrombotic outcomes, SCFAs generally confer vaso-protective and anti-inflammatory benefits. BAs exhibit dual functions, regulating both lipid metabolism and inflammatory signaling through dedicated receptors. The dynamic balance among these metabolites, which is markedly influenced by diet and microbial composition, collectively shapes cardiovascular risk. The present review critically synthesized the current mechanistic evidence on how TMAO, SCFAs and BAs contribute to hypertension, atherosclerosis and heart failure, with the aim to provide a cohesive framework for the development of novel diagnostic and therapeutic strategies.

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Abbreviations: TMAO, trimethylamine N-oxide; SCFAs, short-chain fatty acids; BAs, bile acids; CVDs, cardiovascular diseases; FMO3, flavin-containing monooxygenase 3; CutC/D, choline TMA-lyase and its activating enzyme; GPCRs, G protein-coupled receptors; GPR41/43, G protein-coupled receptor 41/43; Olfr78, Olfactory receptor 78; HDAC, histone deacetylase; FXR, farnesoid X receptor; TGR5, takeda G-protein-coupled receptor 5; BSH, bile salt hydrolase; DCA, deoxycholic acid; MACE, major adverse cardiovascular events; STEMI, ST-segment elevation myocardial infarction; FMT, fecal microbiota transplantation

Key words: gut microbiota, gut-heart axis, trimethylamine n-oxide, short-chain fatty acids, bile acids, atherosclerosis, hypertension, heart failure

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1. Introduction

The human gut is inhabited by a dense and metabolically active group of microorganisms, including bacteria, archaea, viruses and fungi, collectively known as the gut microbiota (1). This complex ecosystem, comprising trillions of microbial cells, possesses a collective genome that markedly outnumbers the human genome and encodes a diverse array of enzymes capable of metabolizing both dietary components and host-derived compounds (2). The resulting chemical products, termed gut microbial metabolites, enter the systemic circulation and act as notable signaling molecules, orchestrating a bidirectional communication network between the gut and distant organs. Over the years, this 'gut-organ' axis has been recognized as a fundamental regulator of host physiology and a marked contributor to the pathogenesis of numerous non-communicable diseases, most notably cardiovascular diseases (CVDs) (3,4).

The concept of a 'gut-heart axis' has evolved from early observations of dysbiosis in disease states to a sophisticated mechanistic framework in which specific microbial metabolites are identified as key drivers of cardiovascular pathology (5). Seminal research has shifted the paradigm from viewing the gut solely as a digestive organ to recognizing it as an endocrine-like system influencing vascular health, cardiac function and thrombotic risk (6,7). This conceptual evolution is supported by a growing body of evidence from both animal models and human cohorts. For instance, preclinical studies have demonstrated that alterations in the gut microbiota can directly influence outcomes after ischemic events such as stroke or angioplasty, modulating inflammation and tissue repair processes (8,9). In clinical settings, distinct microbial and metabolic signatures have been consistently associated with major cardiovascular conditions, including hypertension, atherosclerosis and heart failure (10-12). The recognition of this axis has thus opened a new frontier for understanding residual cardiovascular risk that is not explained by traditional risk factors alone.

The present review focuses on three major classes of gut microbiota-derived metabolites that have emerged as central players in the gut-heart axis: Trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs) and bile acids (BAs). TMAO, a pro-atherogenic and pro-thrombotic molecule derived from dietary choline and carnitine, has been extensively studied and linked to adverse cardiovascular outcomes (13,14). Conversely, SCFAs, primarily acetate, propionate and butyrate, are produced from the fermentation of dietary fiber and are largely considered cardioprotective, exerting anti-inflammatory and blood pressure-lowering effects (15,16). BAs, traditionally known for their role in lipid digestion, are now appreciated as signaling hormones that regulate systemic metabolism and inflammation through dedicated receptors, with their composition being shaped by microbial enzymes (17,18). The balance between these metabolite classes appears critical; a metabolic milieu characterized by high TMAO and low SCFAs, for instance, is increasingly recognized as a hallmark of cardiovascular pathology (19,20).

Despite the wealth of data on individual metabolites, to the best of our knowledge a comprehensive and integrated synthesis of their roles in specific cardiovascular diseases is needed. Early research largely centered on the detrimental effects of TMAO, but it is now known that SCFAs and BAs exert parallel and often counter-regulatory influences (21). For example, certain therapeutic interventions targeting one pathway invariably affect the others, as seen with statins or berberine, which modulate both TMAO production and SCFAs/BA profiles (22,23). Therefore, the primary objective of the present review was to move beyond a TMAO-centric view and provide a critical, up-to-date synthesis of how these three key metabolite classes (TMAO, SCFAs and BAs) mechanistically contribute to the pathophysiology of hypertension, atherosclerosis and heart failure. By critically evaluating their distinct and interconnected signaling pathways, the present review aimed to clarify their potential as both biomarkers for risk stratification and targets for novel therapeutic strategies, ultimately providing a cohesive framework for clinicians and researchers navigating this rapidly advancing field.

2. TMAO: From dietary precursor to pro-atherogenic mediator

The gut microbial metabolite TMAO has emerged as a marked mechanistic link between dietary patterns, gut microbiota composition and the pathogenesis of CVDs (13). Its generation involves a coordinated host-microbiome pathway, and elevated circulating levels are consistently associated with adverse cardiovascular outcomes through diverse biological mechanisms. The present section critically reviews the biosynthesis, pathophysiological roles and clinical evidence pertaining to TMAO. Table I provides a comprehensive summary of the TMAO pathway, encompassing its dietary sources, key microbial and host enzymes, proposed mechanisms in cardiovascular pathology and potential therapeutic targets.

Biosynthesis pathway: A collaborative host-microbiome effort. The production of TMAO is a metaorganismal process initiated by the ingestion of dietary precursors rich in trimethylamine (TMA)-containing compounds, such as choline, L-carnitine and phosphatidylcholine, notably found in red meat, eggs and certain fish (24,25). Gut microbiota possessing specific enzymes, notably choline TMA-lyase (CutC) and its activating enzyme CutD, catalyze the conversion of these dietary substrates into TMA (26,27). Ramireddy *et al* demonstrated that the abundance of the *cutC* gene, particularly within Enterobacteriaceae, is directly associated with increased urinary TMAO levels, highlighting the genetic basis of microbial TMA production (27). Following absorption into the portal circulation, TMA is transported to the liver where it is rapidly oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3) (28). Catucci *et al* (28) developed a direct assay to measure human FMO3 activity, providing a tool to study interindividual variability in this notable host metabolic step. Genetic variants in the FMO3 gene notably influence enzymatic efficiency and plasma TMAO concentrations, as detailed by Phillips and Shephard, with specific common loss-of-function mutations (predominantly including missense and nonsense mutations such as p.Pro153Leu and p.Glu305X) causing trimethylaminuria, a condition characterized by impaired TMA oxidation (29). Conversely, gain-of-function variants or increased FMO3 expression can enhance TMAO production, potentially elevating CVDs risk (30,31). A schematic overview of the TMAO generation pathway and its proposed mechanisms in CVDs is presented in Fig. 1.

Mechanistic insights into TMAO-driven pathogenesis. Extensive preclinical studies have delineated multiple pro-atherogenic and pro-thrombotic mechanisms by which TMAO exacerbates cardiovascular pathology. TMAO promotes endothelial dysfunction by inducing oxidative stress and reducing nitric oxide bioavailability. Brunt *et al* (32) reported that TMAO administration promotes age-related vascular oxidative stress and endothelial dysfunction in both mice and healthy humans. Furthermore, TMAO enhances foam cell formation by upregulating scavenger receptors on macrophages, facilitating the uptake of oxidized low-density lipoprotein (33,34). It also directly stimulates inflammatory pathways, such as the NLRP3 inflammasome, leading to the

Table I. Key preclinical and clinical evidence of gut metabolites in CVD.

Author, year	Model/ population	Target metabolite	Disease/condition	Intervention/observation	Key findings	(Refs.)
Kaye *et al*, 2020	Mice	SCFAs	Hypertension/ hypertrophy	Fiber-deficient diet vs. supplementation	Fiber deficiency drives hypertension; acetate/propionate reversal.	(15)
Li *et al*, 2021	Mice	TMAO	Atherosclerosis	Berberine treatment	Berberine attenuates atherosclerosis by inhibiting microbial TMA/TMAO production.	(22)
Brunt *et al*, 2020	Mice/human	TMAO	Vascular aging	TMAO supplementation	Induces oxidative stress and endothelial dysfunction; reduces NO bioavailability.	(32)
Benson *et al*, 2023	Mice/human	TMAO	Aortic aneurysm	TMAO levels/diet	TMAO promotes abdominal aortic aneurysm via inflammatory/apoptotic mechanisms.	(36)
Yang *et al*, 2019	Mice/cells	TMAO	Cardiac fibrosis	TMAO exposure	Accelerates fibroblast-to-myofibroblast differentiation and fibrosis.	(37)
Tang *et al*, 2021	Human (EPIC-Norfolk)	TMAO	Coronary artery disease	Prospective cohort analysis	Elevated plasma TMAO predicts future CAD risk in apparently healthy individuals.	(46)
Tan *et al*, 2019	Human (STEMI)	TMAO	Myocardial infarction	Clinical biomarker analysis	TMAO is a novel biomarker for plaque rupture in patients with STEMI.	(47)
Suzuki *et al*, 2019	Human (BIOSTAT-CHF)	TMAO	Heart failure	Clinical cohort analysis	Higher TMAO associated with increased mortality and hospitalization in HF.	(48)
Crimarco *et al*, 2020	Human	TMAO	CVD risk factors	Plant-based vs. animal meat diet	Plant-based meat alternatives significantly reduced TMAO levels.	(53)
Pathak *et al*, 2020	Mice	TMAO	Lipid metabolism	Small molecule CutC inhibition	Inhibiting microbial TMA production alters host cholesterol and BA metabolism.	(54)
Organ *et al*, 2020	Mice (HF model)	TMAO	Heart failure	Nonlethal CutC inhibition	Inhibition of TMAO production improved cardiac function and remodeling.	(55)
Haghikia *et al*, 2022	Mice/human	Propionate	Atherosclerosis	Propionate supplementation	Attenuates atherosclerosis via immune-dependent regulation (Tregs).	(61)
Muralitharan *et al*, 2025	Mice	SCFAs	Hypertension	GPR41/43 knockout	Host GPR41/43 sensing is essential for the antihypertensive effect of metabolites.	(62)
Bartolomaeus *et al*, 2019	Mice	Propionate	Hypertension	Propionate treatment	Protects against hypertensive damage by mitigating systemic immune activation.	(66)
Onyszkiewicz *et al*, 2019	Rats	Butyrate	Hypertension	Colonic butyrate administration	Lowers BP via afferent colon-vagus nerve signaling and GPR41/43.	(68)

Table I. Continued.

Author, year	Model/ population	Target metabolite	Disease/condition	Intervention/observation	Key findings	(Refs.)
Song *et al*, 2021	Rats	Butyrate	Myocardial Infarction	Butyrate administration	Improves post-MI tissue repair via HDAC inhibition and anti-inflammatory effects.	(69)
Ma *et al*, 2023	Mice (ApoE-/-)	Butyrate	Atherosclerosis	Butyrate treatment	Suppresses atherosclerotic inflammation via macrophage polarization (GPR43/HDAC).	(70)
Hua *et al*, 2025	Mice	Butyrate	Atherosclerosis	*L. murinus*/*L. johnsonii*	Suppresses macrophage pyroptosis via the Butyrate-GPR109A-GSDMD axis.	(75)
Jama *et al*, 2023	Human (hypertensive)	Acetate/ butyrate	Prebiotic (HAMSAB) trial	Prebiotic fiber lowered systolic blood pressure in patients with untreated hypertension.	HAMSAB significantly reduced 24-h ambulatory systolic and diastolic blood pressure, increased fecal and circulating SCFA levels, and enriched SCFA-producing commensal bacteria (e.g., *Faecalibacterium*, *Roseburia*) in the gut microbiota.	(82)
Pham *et al*, 2024	Mice/rats	SCFAs	Ischemic heart disease	Engineered probiotics	Bacteria secreting SCFAs effectively prevented myocardial injury.	(83)
Fu *et al*, 2023	Mice	BAs	Atherosclerosis	HuangQi ChiFeng decoction	Alleviates atherosclerosis via FXR signaling and maintaining BA homeostasis.	(89)
Qi *et al*, 2025	Mice/human	BAs	Thrombosis	TGR5 activation	TGR5 activation inhibits platelet activation and atherothrombosis.	(92)
Zheng *et al*, 2025	Mice	BAs/ TMAO	Atherosclerosis	*B. animalis* subsp. *lactis*	Improves atherosclerosis by regulating BA metabolism and the TMA-TMAO pathway.	(95)
Chakraborty *et al*, 2023	Rats	Conjugated BAs	Hypertension	Dietary/metabolic analysis	Identified conjugated bile acids as 'nutritionally re-programmable' antihypertensives.	(99)
Nowiński *et al*, 2023	Rats	Deoxy-cholic Acid (DCA)	Hemodynamics	Secondary BA (DCA) administration	DCA increases cardiac output and blood pressure (deleterious hemodynamic effect).	(98)
Zhao *et al*, 2023	Human (STEMI)	BAs	Myocardial Infarction	Prognostic analysis	Gut-derived metabolites (BAs) associate with infarct severity and prognosis.	(101)
Padro *et al*, 2024	Human	BAs	Hyperlipidemia	*L. plantarum* supplementation	Specific probiotic strains modulate bile acids and cholesterol metabolism in humans.	(106)

TMAO, Trimethylamine N-oxide; SCFAs, short-chain fatty acids; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; HF, heart failure; BP, blood pressure; HDAC, histone deacetylase; GPR43, G protein-coupled receptor 43; FXR, farnesoid x receptor; TGR5, takeda G-protein-coupled receptor 5; BAs, bile acids; DCA, deoxycholic acid; MI, myocardial infarction.

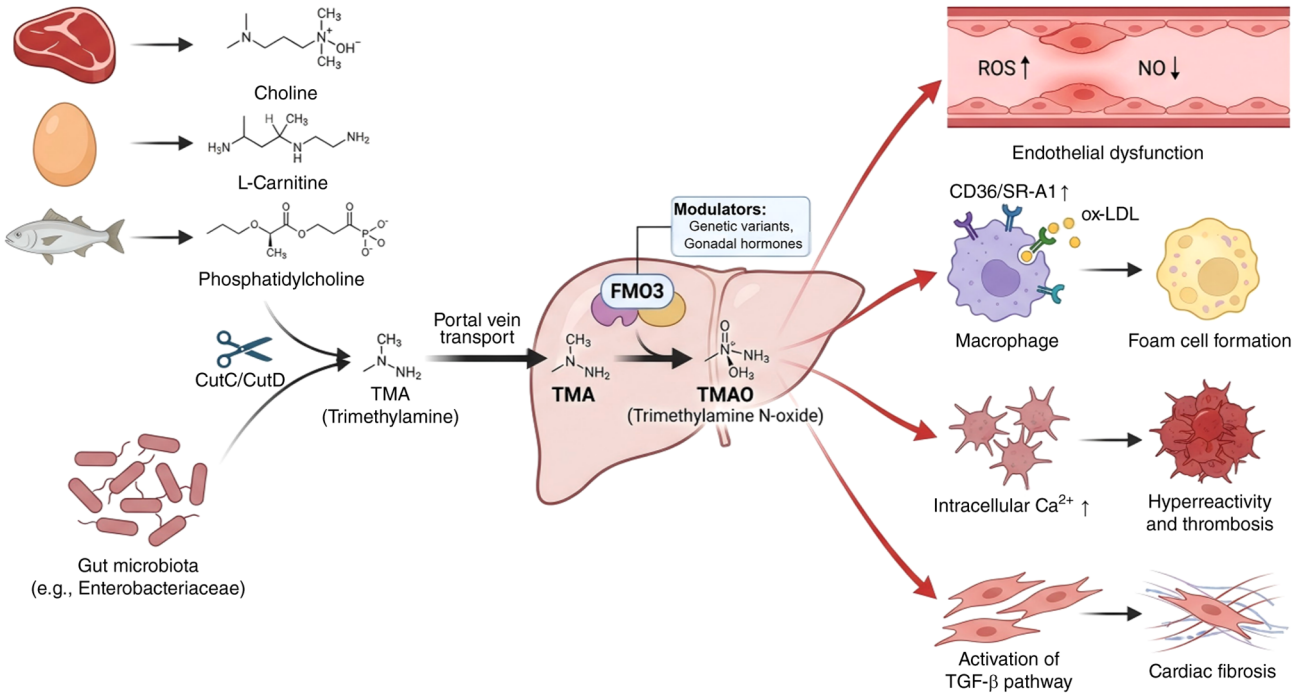

Figure 1. Pathway of TMAO generation and its mechanism in causing cardiovascular diseases. TMAO, trimethylamine N-oxide; TMA, trimethylamine; ox-LDL, oxidated low-density lipoprotein; FMO3, flavin-containing monooxygenase 3; ROS, reactive oxygen species, NO, nitric oxide; CutC/D, choline trimethylamine-lyase.

secretion of pro-inflammatory cytokines (35,36). Beyond atherosclerosis, TMAO contributes to adverse cardiac remodeling and fibrosis. Yang *et al* (37) found that TMAO accelerates fibroblast-to-myofibroblast differentiation, a key process in cardiac fibrosis. Additionally, TMAO induces platelet hyperreactivity and enhances thrombosis potential (38,39). Evidence also implicates TMAO in promoting vascular inflammation and structural changes in conditions such as abdominal aortic aneurysm and pulmonary hypertension (36,40,41).

Beyond the aforementioned direct mechanisms, studies have identified the specific signaling pathways through which TMAO promotes adverse cardiac remodeling. Elevated TMAO levels in pressure-overload-induced heart failure activate the transforming growth factor-β1 (TGF-β1)/Smad3 signaling pathway and the p65 nuclear factor-κB (NF-κB) inflammatory pathway, both of which are notable drivers of cardiac hypertrophy and fibrosis (42). Moreover, TMAO exacerbates cardiac dysfunction by down-regulating Piezo1 expression in cardiomyocytes, a mechanosensitive ion channel essential for maintaining diastolic function, thereby contributing to heart failure with preserved ejection fraction (43). Beyond the well-established pro-inflammatory and pro-thrombotic actions, recent studies have elucidated specific molecular pathways through which TMAO promotes foam cell formation and impairs cholesterol homeostasis. Luo *et al* (34) demonstrated that TMAO promotes oxidative stress and lipid accumulation in macrophage foam cells via the Nrf2/ATP-binding cassette transporter A1 (ABCA1) pathway, wherein TMAO inhibits the expression of the key antioxidant transcription factor Nrf2 and its downstream effectors HO-1 and GPX4, while simultaneously suppressing cholesterol efflux via ABCA1. Consequently, interventions that reduce TMAO levels such as competitive substrate analogs like 3,3-dimethyl-1-butanol (DMB) and natural compounds including berberine (22,42) relieve this inhibitory pressure, restoring Nrf2-mediated antioxidant defense and ABCA1-mediated cholesterol efflux capacity, thereby attenuating atherosclerotic lesion progression. These mechanistic insights have guided the development of TMAO-targeted therapeutic strategies.

Clinical and epidemiological evidence: Associations and prognostic value. A substantial body of observational and prospective cohort studies has established a notable association between elevated plasma TMAO levels and increased risk of major adverse cardiovascular events (MACE), including myocardial infarction, stroke and cardiovascular mortality (44,45). Tang *et al* (46) demonstrated that plasma TMAO levels predict future risk of coronary artery disease in apparently healthy individuals. Similarly, Tan *et al* (47) identified plasma TMAO as a novel biomarker for plaque rupture in patients with ST-segment elevation myocardial infarction (STEMI). In heart failure, Suzuki *et al* (48) analyzing data from the BIOSTAT-CHF cohort, reported an association between higher TMAO levels and worse outcomes, including increased mortality and hospitalization. A subsequent meta-analysis by Li *et al* (49) confirmed the prognostic value of TMAO in heart failure populations.

However, while numerous studies support a detrimental role, some reports present neutral or context-dependent associations. Bjørnestad *et al* (50) found that circulating TMAO levels did not predict 10-year survival in patients with or without coronary heart disease in their cohort. These discrepancies may be attributed to several factors, including differences in population characteristics, dietary habits, renal

function, timing of measurement and specific confounding variables such as age, sex, traditional cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia), concomitant medication use (statins, antibiotics) and baseline renal function (51,52). A critical analysis of the sources of this heterogeneity strengthens interpretive depth. First, renal function is a major confounder, as TMAO is primarily cleared via glomerular filtration and levels rise substantially with declining kidney function (21). Second, inter-individual variability in TMAO metabolism arises from host genetic polymorphisms in FMO3 (29) and differences in the gut microbial abundance of choline TMA-lyase (CutC)-harboring bacteria (27), leading to variable TMA-producing capacity that is independent of dietary precursor intake (13). Third, study design differences, including patient selection (primary vs. secondary prevention), timing of TMAO measurement relative to disease onset and outcome definitions, contribute to disparate findings (44,45). For instance, TMAO consistently predicts atherosclerotic events and plaque rupture (46,47), whereas its association with all-cause mortality is more variable, possibly reflecting differential contributions of thrombotic vs. non-thrombotic pathways across populations (50,52). For instance, Yazaki *et al* (51) highlighted ethnic differences in the association between TMAO and outcomes in patients with acute heart failure. The consistency of the association of TMAO with atherosclerosis and thrombosis across multiple large cohorts lends considerable weight to its role as a risk marker (44,46). By contrast, its predictive power for all-cause mortality in all settings appears more variable, suggesting that TMAO might be a stronger marker of atherosclerotic burden and plaque instability than of generalized mortality risk, or that its effect is modulated by specific disease states (50,52).

Therapeutic strategies: Targeting the TMAO pathway. The elucidation of the TMAO pathway has unveiled several promising therapeutic avenues for CVDs prevention and treatment. Strategies can be categorized into dietary modulation, microbial enzyme inhibition and host metabolism interference. Dietary interventions aimed at reducing precursor intake, such as adopting plant-based diets, effectively lower TMAO levels (25,53). Crimarco *et al* (53) showed that replacing animal-based meat with plant-based alternatives markedly reduced TMAO and other CVD risk factors including low-density lipoprotein cholesterol (LDL-C), total cholesterol and systolic blood pressure. Direct inhibition of microbial TMA production represents a targeted approach. Pathak *et al* (54) identified iodomethylcholine, a small molecule inhibitor of gut microbial choline TMA-lyase (CutC), which altered host cholesterol and BA metabolism by promoting fecal neutral sterol excretion, enhancing hepatic cholesterol catabolism via de-repression of the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1), and shifting the circulating bile acid pool toward increased conjugated bile acids (particularly tauro-β-muricholic acid) with concomitant reduction in intestinal farnesoid X receptor (FXR) signaling in mice, demonstrating proof-of-concept. Similarly, Organ *et al* (55) reported that non-lethal inhibition of gut microbial TMAO production via oral administration of the competitive choline analog DMB (1.0% in drinking water for 6 weeks) improved cardiac function and remodeling in a murine model of heart failure.

To further elaborate on the mechanistic basis of CutC inhibition, Pathak *et al* (54) demonstrated that pharmacological inhibition of gut microbial choline TMA-lyase activity in mice not only reduces TMAO production but also markedly alters host cholesterol and BA metabolism (54). Specifically, CutC inhibition leads to a notable reduction in circulating TMAO levels, which in turn suppresses hepatic FMO3 expression. The consequent decrease in FMO3 activity promotes fecal neutral sterol loss and increases circulating levels of conjugated BAs, particularly tauro-β-muricholic acid (54). These changes reduce intestinal FXR signaling, thereby de-repressing the rate-limiting enzyme in the classic BA synthesis pathway, CYP7A1, and enhancing overall cholesterol catabolism (54). Thus, the metabolic benefits of CutC inhibition extend beyond TMAO reduction to include favorable remodeling of the enterohepatic circulation of BAs.

Pharmacological agents and natural compounds can also modulate the pathway. Li *et al* (22) demonstrated that berberine attenuates choline-induced atherosclerosis by inhibiting TMA and TMAO production via gut microbiome manipulation. Probiotic supplementation has shown potential, with Ramireddy *et al* (56) identifying *Lactobacillus amylovorus* LAM1345, *Lactiplantibacillus plantarum* LP1145 and *Limosilactobacillus fermentum* LF33 (administered as a multistrain formula at 10^9 CFU/ml) as specific probiotic strains capable of markedly reducing serum TMAO levels in choline-fed C57BL/6 mice, although human meta-analyses indicate a more modest and variable effect (56,57). Finally, enhancing TMAO clearance through modulation of renal organic ion transporters (e.g., organic cation transporters and multidrug resistance proteins) to facilitate urinary excretion or direct dialytic removal in patients with advanced kidney disease, and blocking its downstream cellular effects via pharmacological inhibition of the NLRP3 inflammasome, activation of the Nrf2 antioxidant pathway, and suppression of platelet hyperreactivity are areas of active investigation (58,59). The collective evidence suggests that a multi-pronged strategy, potentially combining dietary changes with selective microbial inhibitors, may offer an effective approach to mitigating the cardiovascular risk associated with this gut-derived metabolite.

The mechanisms by which inhibition of TMA and TMAO production attenuates choline-induced atherosclerosis involve a coordinated multi-level cascade. At the microbial stage, pharmacological inhibition of CutC using small molecules such as iodomethylcholine directly blocks the conversion of choline to TMA. This inhibition not only reduces circulating TMAO levels but also triggers a cascade of favorable metabolic remodeling, including suppression of hepatic FMO3 expression, increased fecal neutral sterol loss and elevated circulating conjugated BAs such as tauro-β-muricholic acid. The resulting reduction in intestinal FXR signaling de-represses CYP7A1, enhancing cholesterol catabolism and excretion (54). At the host metabolic stage, reducing TMAO levels relieves TMAO-mediated suppression of the Nrf2/ABCA1 pathway in macrophages, restoring both antioxidant capacity and reverse cholesterol transport (34). Natural compounds such as berberine exert dual effects by remodeling gut microbiota composition to reduce the abundance of TMA-producing bacteria and by directly inhibiting

CutC/D enzyme activity, as demonstrated by Ma *et al* (60) who described a 'vitamin-like' effect of berberine in down-regulating the choline-TMA-TMAO production pathway (60). In addition to direct enzymatic inhibitors, several classes of gut microbial TMAO production inhibitors have been shown to improve cardiac function and remodeling in murine heart failure models (42). Structural analogs of choline, most notably DMB, competitively inhibit microbial cutC/D activity and reduce TMAO generation without exerting bactericidal effects. In a pressure overload induced heart failure model, oral administration of DMB (1.0% in drinking water for 6 weeks) notably lowered plasma TMAO levels, attenuated adverse cardiac structural remodeling (including cardiac hypertrophy and fibrosis), suppressed ventricular inflammation and reduced susceptibility to ventricular arrhythmia. Mechanistically, the cardioprotective effects of DMB are mediated through down-regulation of the p65 NF-κB inflammatory pathway and the TGF-β1/Smad3 signaling pathway, both of which are marked drivers of cardiac hypertrophy and fibrosis in pressure overloaded hearts (42). These findings, together with the effects of iodomethylcholine and berberine, establish that targeted reduction of gut microbial TMAO production, whether through direct CutC inhibition or competitive substrate analog strategies, represents a viable multipronged therapeutic approach for mitigating TMAO driven cardiovascular pathology in heart failure. Collectively, these converging mechanisms establish the TMAO generation cascade as a tractable therapeutic target for atherosclerosis prevention and treatment.

Finally, strategies to enhance TMAO clearance represent an active area of investigation, including modulation of renal organic ion transporters (such as organic cation transporters and multidrug resistance proteins) to facilitate urinary excretion, as well as direct dialytic removal of TMAO in patients with advanced kidney disease (58,59). Concurrently, blocking downstream cellular effects constitutes a complementary therapeutic approach, with ongoing studies focusing on pharmacological inhibition of the NLRP3 inflammasome to reduce pro-inflammatory cytokine secretion, activation of the Nrf2 antioxidant pathway to counteract TMAO-induced oxidative stress and suppression of platelet hyperreactivity to mitigate thrombosis risk (35,36,38,39). These 'TMAO resistance' strategies aim to attenuate pathological consequences even when TMAO synthesis cannot be fully suppressed (58).

3. SCFAs: Microbial fermentation products with cardioprotective potential

In contrast to the generally deleterious effects of TMAO, SCFAs (primarily acetate, propionate and butyrate) represent a class of gut microbiota-derived metabolites that exert pleiotropic protective effects on the cardiovascular system (61,62). These metabolites serve as notable signaling molecules bridging the gut environment with host physiology, influencing blood pressure, inflammation and metabolic homeostasis (61,62). As the field advances from associative studies to mechanistic elucidation, evidence highlights SCFAs as promising targets for 'postbiotic' interventions. The following section synthesize current knowledge on their production, molecular mechanisms and roles in specific cardiovascular pathologies, while critically evaluating the translational potential of these findings.

Production and types: Acetate, propionate, butyrate from dietary fiber fermentation. SCFAs are the primary end-products of the anaerobic fermentation of non-digestible dietary fibers and resistant starches by commensal bacteria in the cecum and colon. The concentration and ratio of these metabolites, predominantly acetate (C2), propionate (C3) and butyrate (C4), are regulated by the composition of the gut microbiome and substrate availability (63,64). While acetate is the most abundant SCFAs in the systemic circulation, butyrate serves principally as the major energy source for colonocytes, maintaining gut barrier integrity and preventing the translocation of pro-inflammatory endotoxins (65). Propionate, largely metabolized by the liver, plays a notable role in regulating gluconeogenesis and cholesterol synthesis (61). A disruption in the production of these metabolites, often driven by a low-fiber 'Western' diet, has been linked to the loss of cardiovascular protection, creating a predisposition to hypertensive and ischemic injuries (15).

Molecular mechanisms of SCFAs action. The cardioprotective effects of SCFAs are mediated primarily through two distinct but interconnected pathways: The activation of G protein-coupled receptors (GPCRs) and the epigenetic regulation of gene expression via histone deacetylase (HDAC) inhibition.

Receptor-mediated signaling: GPCRs. SCFAs function as ligands for specific GPCRs, notably GPR41 (FFAR3), GPR43 (FFAR2) and olfactory receptor 78 (Olfr78), which are expressed across various tissues including the vasculature, kidneys and immune cells. Bartolomaeus *et al* (66) provided seminal evidence that propionate protects against hypertensive cardiovascular damage by mitigating systemic immune activation, an effect largely dependent on regulatory T cells modulation. Recent single-cell atlas analyses have further mapped the expression of these receptors in the heart, confirming their direct relevance to cardiac physiology (67). Mechanistically, the activation of GPR41 and GPR43 by SCFAs has been shown to lower blood pressure (62), although the precise pathway remains a subject of investigation. While earlier studies implicated Olfr78 in the renal juxtaglomerular apparatus as a mediator of renin release (15,16), more recent work by the Marques group indicates that G protein-coupled receptor 41/43 (GPR41/43) signaling is essential for the antihypertensive efficacy of gut microbial metabolites (62). Furthermore, Onyszkiewicz *et al* (68) proposed a gut-neural axis, demonstrating that butyrate may lower blood pressure via afferent colon-vagus nerve signaling rather than solely through direct vascular relaxation. This suggests a complex mode of action involving both systemic circulation and neural reflexes.

Epigenetic regulation: HDAC inhibition. Beyond receptor signaling, butyrate and propionate act as potent inhibitors of HDACs, thereby promoting the acetylation of histone proteins and facilitating the transcription of cardioprotective genes. This epigenetic mechanism is particularly crucial in mitigating pathological remodeling. For instance, Song *et al* (69) demonstrated that butyrate administration improved tissue repair following myocardial infarction by inhibiting HDACs, which in turn suppressed pro-inflammatory cytokine production and reduced fibrosis. Similarly, Ma *et al* (70) reported that butyrate suppresses atherosclerotic inflammation by modulating

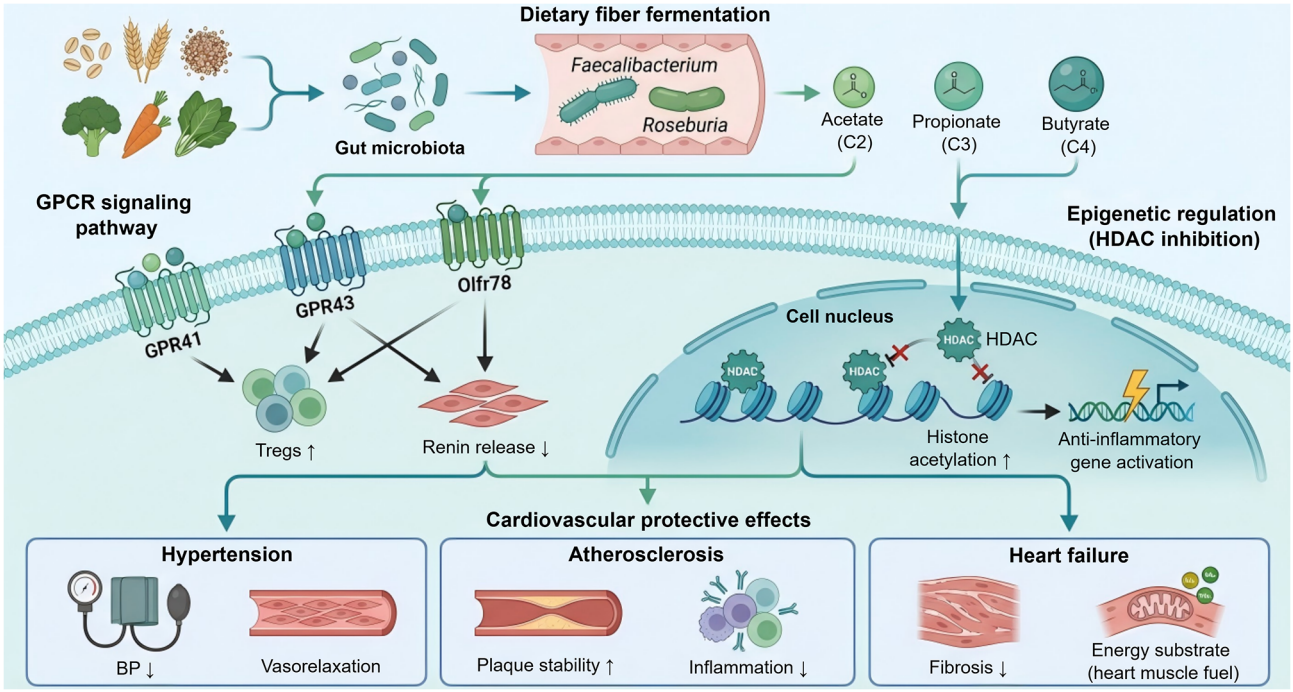

Figure 2. Multiple major cardiac protection pathways of short chain fatty acids. BP, blood pressure; Tregs, regulatory T cells; HDAC, histone deacetylase.

macrophage polarization via a GPR43-HDAC axis. This dual mechanism, simultaneous receptor activation and epigenetic modulation, allows SCFAs to exert marked anti-inflammatory and anti-fibrotic effects (71), providing a robust counterbalance to the pro-inflammatory drive of dysbiosis. The major cardioprotective pathways mediated by SCFAs are summarized in Fig. 2.

Role in specific CVDs

Hypertension. The relationship between SCFAs deficiency and hypertension is among the most well-characterized links in the gut-heart axis. A study by Kaye *et al* (15) revealed that a deficiency in prebiotic fiber and the subsequent lack of SCFAs signaling leads to the development of hypertension and cardiac hypertrophy. Experimental supplementation with propionate or acetate has consistently shown efficacy in reversing these phenotypes. Bartolomaeus *et al* (66) observed that propionate attenuated cardiac hypertrophy and fibrosis in angiotensin II-infused mice, highlighting the immunomodulatory role of SCFAs in hypertensive end-organ damage. Notably, sex-specific differences have been noted; Hsu *et al* (72) found that maternal acetate supplementation could reverse programmed hypertension in male offspring, while no statistically significant antihypertensive effect was observed in female littermates under identical experimental conditions, suggesting a developmental origin of sex-specific SCFAs sensitivity. However, translational success may vary based on genetic background. Jama *et al* (73) cautioned that while prebiotic fiber is beneficial, it may not fully override strong genetic predispositions to heart failure, indicating that SCFAs interventions might need to be personalized based on host genetics.

Atherosclerosis. In the context of atherosclerosis, SCFAs appear to stabilize plaques and reduce lesion volume by modulating cholesterol metabolism and immune responses. Haghikia *et al* (61) elucidated a gut-immune axis where propionate increased regulatory T cell numbers and reduced cholesterol burden, thereby attenuating atherosclerotic lesion formation. This finding challenges the traditional lipid-centric view by integrating immune regulation. Conversely, Brandsma *et al* (74) demonstrated that a pro-inflammatory microbiota accelerates atherosclerosis, reinforcing the concept that the balance between pro-inflammatory dysbiosis and anti-inflammatory SCFAs production is critical. Furthermore, recent evidence by Hua *et al* (75) suggests that butyrate can suppress macrophage pyroptosis via the GPR109A-Gasdermin D pathway, offering a novel mechanistic explanation for plaque stabilization. The interplay between SCFAs and other metabolites is also notable; for example, Li *et al* (76) found that pharmacological interventions could alleviate atherosclerosis by simultaneously restructuring the gut microbiota to enhance SCFAs production while suppressing potential toxins.

Heart failure. Emerging evidence suggests that SCFAs may serve as an alternative energy substrate for the failing heart and a regulator of adverse remodeling. Tang *et al* (77) highlighted the necessity of an intact gut microbiota for post-infarction cardiac repair, as microbiota-depleted mice exhibited impaired immune responses and rupture. Supplementation with SCFAs has been shown to improve outcomes in heart failure models by attenuating mitochondrial dysfunction and ferroptosis (78). Moreover, clinical data from the BIOSTAT-CHF cohort and others indicate an association between altered gut microbial metabolites and heart failure severity (79,80). While the direct inotropic effects of SCFAs are debated, their ability to reduce systemic afterload (via blood pressure reduction) and suppress myocardial inflammation positions them as valuable adjunctive therapeutics in heart failure management (81).

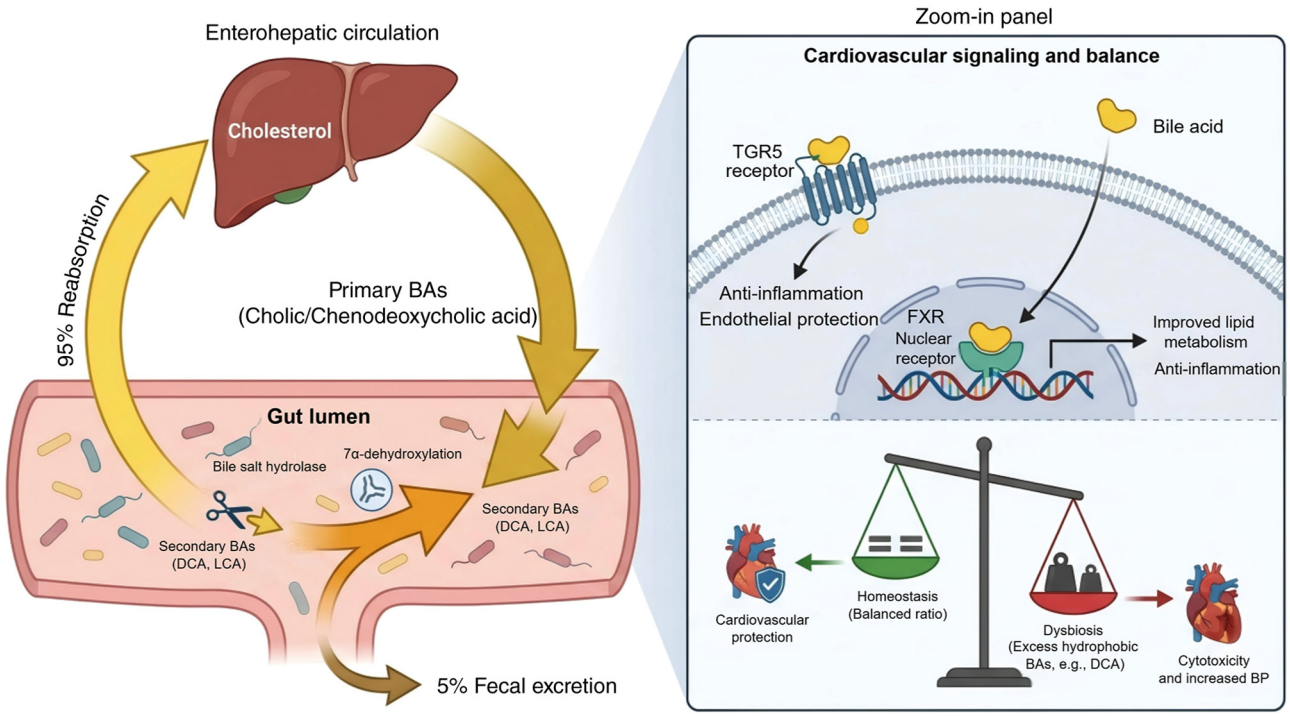

Figure 3. Enterohepatic circulation and signal transduction of bile acids. BP, blood pressure; DCA, deoxycholic acid; FXR, farnesoid X receptor.

Clinical translation: Challenges and opportunities. Translating the notable preclinical benefits of SCFAs into human clinical practice presents both opportunities and challenges. High-fiber diets are the most accessible strategy to boost endogenous SCFAs production, yet patient adherence and inter-individual variability in microbiome composition often limit efficacy (82). The Phase II randomized trial by Jama *et al* (82) using acetylated and butyrylated high-amylose maize starch provided proof-of-concept that targeted prebiotic interventions can lower blood pressure in patients with untreated hypertension. However, the short half-life of orally administered SCFAs remains a pharmacokinetic hurdle. Novel delivery systems, such as engineered probiotics designed to constitutively secrete SCFAs (83), are currently under investigation to provide sustained therapeutic levels. Future clinical strategies should move beyond generic fiber recommendations to personalized 'precision biotic' approaches that account for the baseline microbiome functional capacity of the patient (84). Studies highlighting the cardioprotective effects of SCFAs in hypertension, atherosclerosis and heart failure are also compiled in Table I, complementing the aforementioned mechanistic discussions.

4. BAs: Dual roles as digestive surfactants and systemic signaling molecules

BAs have traditionally been viewed solely as digestive surfactants that facilitate the emulsification and absorption of dietary lipids and fat-soluble vitamins (85,86). However, contemporary research has redefined BAs as potent steroid hormones that regulate systemic metabolic homeostasis and cardiovascular function through specific receptors. The size and composition of the BA pool are dynamically regulated by the gut microbiota, which transforms primary BAs synthesized in the liver (cholic acid and chenodeoxycholic acid) into secondary BAs [such as deoxycholic acid (DCA) and lithocholic acid] within the distal intestine. This metabolic interplay creates a complex signaling network known as the gut-liver-heart axis. The following sections explore the mechanisms of microbial BA transformation, the receptor-mediated pathways influencing cardiovascular pathology, and the therapeutic potential of targeting this axis. Fig. 3 illustrates the enterohepatic circulation of BAs and the downstream effects of FXR and Takeda G-protein-coupled Receptor 5 (TGR5) activation on vascular endothelial cells and cardiomyocytes.

Microbial transformation and regulation of the BA pool. The diversity of the circulating BA pool is dictated by the enzymatic capacity of the intestinal microbiome. A notable initial step in this process is catalyzed by bile salt hydrolase (BSH), an enzyme prevalent in various commensal genera including *Lactobacillus* and *Bifidobacterium*. BSH liberates the glycine or taurine amino acid from the steroid core of conjugated BAs, rendering them susceptible to further modification. Song *et al* (85) and Jia *et al* (86) utilized metagenomic sequencing to demonstrate that the abundance and diversity of BSH genes are markedly associated with host health, while a reduction in BSH activity is frequently observed in metabolic disorders. Following deconjugation, 7α-dehydroxylation converts primary BAs into secondary BAs, which are more hydrophobic and cytotoxic. Recent evidence suggests that this microbial transformation is not merely a waste-disposal process but a regulatory mechanism for host cholesterol levels. For instance, Liu *et al* (87) identified that specific *Lactobacillus* strains modulate cholesterol levels by regulating *Bifidobacterium pseudolongum* via BSH activity, thereby

altering the hydrophobicity of the BA pool and influencing fecal excretion; however, dysbiosis can disrupt this balance. Aging and high-fat diets have been shown to alter the BA profile towards a pro-inflammatory phenotype characterized by elevated secondary BAs, which Majait *et al* (88) link to impaired postprandial metabolism. This shift highlights that the microbial enzymatic machinery is a determinant factor in maintaining a cardioprotective BA profile.

Signaling mechanisms: FXR and TGR5 pathways. The enterohepatic circulation of BAs and their key signaling pathways mediated by FXR and TGR5 are illustrated in Fig. 3. The cardiovascular effects of BAs are primarily mediated through the nuclear receptor FXR and the membrane-bound receptor TGR5 (GPBAR1), both of which are widely expressed in vascular endothelial cells, smooth muscle cells, and cardiomyocytes, and exert pleiotropic regulatory effects on vascular function, inflammation, and cardiac remodeling (89-91). Activation of FXR has been generally associated with anti-inflammatory and lipid-lowering effects. Fu *et al* (89) demonstrated that HuangQi ChiFeng decoction alleviates atherosclerosis by inhibiting intestinal FXR signaling. Specifically, this decoction reduces levels of FXR agonists (chenodeoxycholic acid, lithocholic acid and DCA), thereby suppressing the FXR/LXRα axis and upregulating hepatic BA synthetic enzymes CYP7A1 and CYP8B1. This promotes BA neosynthesis and cholesterol catabolism, ultimately reducing hepatic lipid accumulation and atherosclerotic lesion formation. Similarly, Marchianò *et al* (90) revealed that defective BA signaling promotes vascular dysfunction, suggesting that FXR agonism could reverse endothelial damage in non-alcoholic fatty liver disease models. These findings are consistent with the work of Zhu *et al* (91), who showed that BSH-active *Lactobacillus johnsonii* lowers cholesterol specifically through an FXR-dependent pathway.

In parallel, TGR5 signaling exerts potent anti-inflammatory effects on macrophages and endothelial cells. Qi *et al* (92) established a critical link between the gut microbiota, BAs and thrombosis. They demonstrated that TGR5 activation inhibits platelet activation and subsequent atherothrombosis, identifying this receptor as a key target for preventing cardiovascular events. Furthermore, Zhang *et al* (93) reported that ursodeoxycholic acid derivatives modulate microglial inflammation via TGR5 signaling following ischemic injury. While both receptors generally mediate protective effects, the specific outcome depends on the ligand affinity, which is determined by the microbial modification of the BA structure. This complexity is further illustrated by findings from distinct studies, where certain secondary BAs may act as antagonists or weak agonists, potentially exacerbating pathology if the primary-to-secondary ratio is dysregulated (92,93).

Pathophysiological roles in CVD

Atherosclerosis and lipid metabolism. The contribution of BAs to atherosclerosis extends beyond simple cholesterol elimination. Dysregulated BA metabolism is a hallmark of atherosclerotic progression, often driven by a gut microbiota incapable of maintaining appropriate signaling metabolite levels. Multiple studies have confirmed that interventions capable of remodeling the gut microbiota to favor specific BA profiles result in reduced plaque burden. For example, Liang *et al* (94) and Zheng *et al* (95) observed that *Bifidobacterium animalis* subspecies alleviate atherosclerosis by modulating the BA profile, which subsequently downregulates intestinal FXR or disrupts the TMA-TMAO pathway. This suggests a crosstalk between BA metabolism and other risk factors such as TMAO. Moreover, chemical derivatization studies by Liao *et al* (96) have enabled precise quantification of these metabolites in human plasma, confirming their association with CVD severity. However, conflicting data exist regarding specific metabolites; while some secondary BAs are atheroprotective via TGR5, high concentrations of hydrophobic BAs such as DCA may damage the gut barrier and promote systemic inflammation, as suggested by findings in models of chronic kidney disease (97). Thus, the therapeutic goal is not simply to increase total BAs but to optimize the profile of specific signaling molecules. A deeper exploration of contradictory findings reveals that even a single secondary BA, DCA, can exert dual effects depending on context. On one hand, DCA activates TGR5, suppressing platelet activation and atherothrombosis (92). On the other hand, elevated DCA levels are independently associated with adverse outcomes in chronic kidney disease (97), and DCA administration in rats increases cardiac output and blood pressure through direct positive inotropic effects (98). These observations indicate that the net cardiovascular impact of DCA is dose-, context- and disease-dependent, highlighting the need to move beyond simplistic classification of bile acids as uniformly protective or harmful.

Hypertension. The regulation of blood pressure by BAs involves complex interactions between vascular tone and renal handling of sodium. Emerging evidence indicates that specific BAs can influence vascular resistance. Chakraborty *et al* (99) proposed that conjugated BAs serve as 'nutritionally reprogrammable' antihypertensive metabolites, challenging the view that only unconjugated forms are bioactive. Conversely, Nowiński *et al* (98) reported that DCA increases cardiac output and blood pressure in rats, highlighting the potential deleterious hemodynamic effects of excess secondary BAs. This disparity underscores the importance of the microbial enzymatic steps that determine the ratio of conjugated to unconjugated and primary to secondary forms. Furthermore, Yu *et al* (100) elucidated a pathway where traditional Chinese medicine granules lower blood pressure via the FXR-FGF15-CYP7A1 axis, reinforcing the concept that systemic blood pressure regulation is tightly coupled to hepatic BA synthesis rates regulated by gut-derived signals.

Heart failure and ischemic injury. In the context of heart failure and myocardial infarction, BAs function as metabolic modulators that can influence cardiac remodeling and survival. Zhao *et al* (101) identified gut microbiota-derived metabolites as notable prognostic markers in patients with STEMI, suggesting that circulating BA levels associate with infarct severity. Mechanistically, Li *et al* (102) demonstrated that specific interventions could revive cardiac function in hypertensive heart failure rats by optimizing microbial-host co-metabolism. Additionally, Shi *et al* (103) found that targeted modulation of the gut microbiota-bile acid axis through probiotic administration and dietary fiber supplementation attenuated chronic heart failure, likely by reducing systemic

inflammation and improving metabolic efficiency. These studies collectively suggest that targeting BA metabolism may offer a novel adjunctive strategy for managing post-infarction remodeling and heart failure progression.

Therapeutic implications and future directions. The reversibility of the gut microbiota offers a promising avenue for therapeutic intervention in CVDs through the modulation of BA metabolism. Dietary strategies, particularly the consumption of specific fibers and polyphenols, have shown robust efficacy in preclinical models. For instance, Ye *et al* (104) and Balderas *et al* (105) demonstrated that anthocyanin-enriched foods and specific fruit intakes modulate the microbiota to favor antihypertensive and lipid-lowering BA profiles. Probiotic supplementation represents another direct approach; Padro *et al* (106) reported in a human trial that specific *Lactobacillus plantarum* strains could effectively enhance intestinal BSH activity to promote deconjugation of glycine- and taurine-conjugated bile acids, increase fecal excretion of neutral sterols and bile acids and downregulate intestinal FXR signaling to upregulate hepatic CYP7A1 expression, thereby modulating cholesterol and BA metabolism

Beyond diet and probiotics, pharmacological targeting of the BA system is advancing. Shah *et al* (107) outlined the rationale for the MYSTIC trial, which investigates the use of BA sequestrants (colesevelam) in patients with Fontan circulation, representing a translation of these concepts into complex clinical scenarios. Furthermore, novel bioengineering approaches, such as the programmable probiotic consortium described by Yang *et al* (108), enable the precise degradation of cholesterol and modification of BAs in response to high-fat diets. These precision medicine tools may overcome the inter-individual variability observed in earlier trials. Future clinical translation should focus on personalized interventions that account for the baseline microbiome and BA pool composition of the patient to ensure consistent therapeutic outcomes.

5. Comparative analysis and cross-talk among metabolite pathways

Understanding the roles of individual gut-derived metabolites, TMAO, SCFAs and BAs, in CVDs is crucial, yet a holistic view necessitates examining their interrelationships. The production and systemic effects of these metabolites are not isolated but are interconnected processes influenced by shared dietary inputs, microbial ecology and host physiology. This integrated network means that a shift in one metabolite pathway can directly or indirectly influence the others, ultimately shaping the overall cardiovascular risk profile. The following section provide a comparative analysis of these key metabolites, explore their interdependence within the gut microbial ecosystem and discuss how their collective dysregulation creates a synergistic detrimental environment in cardiometabolic diseases. Table II provides a systematic summary of the sources, key receptors, major cardiovascular effects and therapeutic implications for TMAO, SCFAs and BAs.

Comparative summary of key metabolites. The three classes of metabolites, TMAO, SCFAs and BAs, originate from distinct dietary precursors and are processed by specific microbial consortia, leading to divergent, and often opposing, effects on cardiovascular health. TMAO is primarily derived from dietary choline, L-carnitine and phosphatidylcholine found in animal products. Its production relies on microbial enzymes such as CutC/D and host hepatic FMO3 and elevated levels are consistently linked to pro-atherogenic, pro-thrombotic and pro-inflammatory pathways, associating with increased MACE risk (109,110). By contrast, SCFAs, including acetate, propionate and butyrate, are fermentation products of dietary fibers and resistant starches. They mediate cardioprotective effects predominantly through GPCR signaling (such as GPR41/43) and HDAC inhibition, resulting in blood pressure reduction, improved lipid metabolism, attenuated inflammation and enhanced plaque stability (111-113). BAs, synthesized from cholesterol in the liver and further modified by gut microbes, act as signaling molecules via receptors such as the FXR and TGR5. Their effects are nuanced; while FXR activation generally confers anti-inflammatory and lipid-lowering benefits, specific secondary BAs such as DCA can exert detrimental hemodynamic effects (98,99,114). Thus, the cardiovascular impact of the gut metabolome is not dictated by a single metabolite but by the dynamic balance between these protective (SCFAs, certain BAs) and harmful (TMAO, some secondary BAs) signals.

Interdependence and competition within the gut microbial ecosystem. The balance among TMAO, SCFAs and BA pathways is markedly influenced by dietary composition and the resulting structure of the gut microbial community. A primary point of interaction is dietary fiber intake, which serves as a key modulator. High fiber consumption promotes the growth of saccharolytic bacteria (such as *Faecalibacterium, Roseburia*) that produce SCFAs. This shift in community structure can suppress the abundance of proteolytic bacteria involved in generating harmful metabolites. For instance, Zhao *et al* (115) demonstrated that a high-fiber diet attenuates myocardial infarction injury by enhancing SCFAs production and modulating gut microbiota. Conversely, a diet low in fiber but high in animal protein and saturated fat, characteristic of a Western dietary pattern, promotes a microbial environment conducive to TMAO production and a BA pool shifted toward more hydrophobic, potentially cytotoxic secondary BAs (116,117).

Furthermore, direct metabolic competition and cross-regulation exist. The microbial transformation of primary to secondary BAs (such as via 7α-dehydroxylation) and the production of TMA (via CutC) are both anaerobic processes that may compete for microbial resources and niche dominance within the gut. Interventions targeting one pathway often affect others. For example, probiotics or dietary components aimed at reducing TMAO, such as certain *Bifidobacterium* strains or berberine, frequently also modulate BA metabolism and SCFAs profiles (94,118). Zheng *et al* (95) specifically illustrated a mechanistic link by showing that *Bifidobacterium animalis subsp. lactis* could alleviate atherosclerosis by modulating BA metabolism through the TMA-TMAO pathway. Similarly, the BA receptor FXR in the intestine can influence the expression of genes involved in maintaining gut barrier integrity; a compromised barrier may increase the translocation of pro-inflammatory molecules such as lipopolysaccharide, which can exacerbate systemic inflammation and potentially

Table II. Comparative characteristics of key gut metabolites.

Author, year	Study type	Disease model/ subject	Intervention/observation	Key metabolites	Main findings/mechanism	(Refs.)
Gencer *et al*, 2020	Human cohort	Prior myocardial infarction	Observational analysis (PEGASUS-TIMI 54)	TMAO	Elevated TMAO levels are associated with increased risk of cardiovascular death and myocardial infarction.	(109)
Lee *et al*, 2021	Human cohort	Atherosclerotic CVD	Longitudinal observational study	TMAO	Longitudinal measures of plasma TMAO predict the risk of atherosclerotic CVD events in older adults.	(110)
Lee *et al*, 2020	Animal (mice)	Stroke	SCFA supplementation/ microbiota manipulation	SCFAs	Gut microbiota-derived SCFAs promote post-stroke recovery; aged mice show reduced SCFA levels.	(111)
Zuo *et al*, 2022	Animal/cell	Atrial fibrillation	SCFA treatment	SCFAs	Alleviates atrial fibrillation via GPR43/ NLRP3 signaling; links gut dysbiosis to atrial electrical remodeling.	(112)
Zhao *et al*, 2022	Animal (mice)	Myocardial infarction	High-fiber diet	SCFAs	Attenuates MI injury and adverse remodeling by enhancing SCFA production and modulating gut microbiota.	(115)
Rath *et al*, 2021	Human	Aging	Observational	TMAO	Higher TMAO levels with aging are mediated by diet and specific trimethylamine-forming bacteria.	(116)
Wang *et al*, 2022	Animal (mice)	Choline-induced TMAO	*Bifidobacterium* strains supplementation	TMAO	*B. breve* and *B. longum* attenuate choline-induced plasma TMAO production by modulating gut microbiota.	(118)
Ahrens *et al*, 2021	Human	CV risk factors	Lifestyle-based immersion program	SCFA producers	Mitigates CV risk factors and induces shifts in *Lachnospiraceae* and *Faecalibacterium* (barrier integrity).	(119)
Jomard *et al*, 2022	Translational study (healthy human volunteers + mouse aortic rings)	Endothelial function	Acute TMAO administration	TMAO	Acute TMAO exposure impairs endothelial function; highlights direct vascular toxicity.	(122)
Ye *et al*, 2025	Animal (mice)	Hypertension	Anthocyanin-enriched purple potato flour	SCFAs	Modulates gut microbiota and SCFAs to prevent hypertension; highlights diet-metabolite interaction.	(104)

Table II. Continued.

Author, year	Study type	Disease model/ subject	Intervention/observation	Key metabolites	Main findings/mechanism	(Refs.)
Li *et al*, 2022	Human cohort	Acute MI and heart failure	Observational	TMAO	High TMAO levels are associated with poor prognosis in patients with acute myocardial infarction and heart failure.	(124)
Mollar *et al*, 2021	Human	Decompensated heart failure	Observational (SIBO assessment)	TMAO, SCFAs	High TMAO and low SCFA levels are surrogates for small intestinal bacterial overgrowth (SIBO) in heart failure.	(126)
Xie *et al*, 2022	Animal (mice)	Atherosclerosis	Ginsenoside Rc	Metabolites	Ameliorates atherosclerosis via regulating gut microbiota and fecal metabolites, showing multi-target effects.	(127)
Yang *et al*, 2022	Animal (mice)	Atherosclerosis	Guanxinning tablet	Metabolites	Attenuates coronary atherosclerosis via regulating gut microbiota and their metabolites in high-fat diet models.	(128)
Wang *et al*, 2024	Animal (mice)	Atherosclerosis	Ginsenosides	Metabolites	Retards atherogenesis via remodeling host-microbiome metabolic homeostasis (multi-pathway modulation).	(129)
Yang *et al*, 2022	Animal (mice)	Atherosclerosis	Taurine supplementation	TMAO, BAs	Alleviates TMAO-induced atherosclerosis by regulating bile acid metabolism (FXR pathway crosstalk).	(130)

TMAO, Trimethylamine N-oxide; SCFAs, short-chain fatty acids; CVD, cardiovascular disease; CV, cardiovascular; SIBO, small intestinal bacterial overgrowth; FXR, farnesoid x receptor; BAs, bile acids; MI, myocardial infarction; GPR43, G-protein-coupled receptor 43.

influence SCFAs receptor signaling and TMAO-associated endothelial dysfunction (89,119). This interdependence is further illustrated by the finding that pharmacological inhibition of CutC not only reduces TMAO but also upregulates CYP7A1 expression and alters BA composition, demonstrating direct metabolic crosstalk between the TMAO and bile acid pathways (54). Therefore, therapeutic strategies cannot be viewed in isolation; modulating fiber intake or administering a probiotic will likely create ripple effects across the entire gut metabolite network.

Metabolite network in cardiovascular disease: A synergistic detrimental environment. In states of dysbiosis commonly associated with CVDs such as atherosclerosis, heart failure and hypertension, a deleterious metabolite profile often emerges, characterized by the co-existence of high TMAO, low SCFAs and dysregulated BA signatures. This triad creates a synergistic environment that accelerates disease pathogenesis. Elevated TMAO promotes endothelial dysfunction, oxidative stress and platelet hyperreactivity (120-122). Concurrently, a deficiency in SCFAs, particularly butyrate and propionate, removes a notable brake on inflammation and vascular tone regulation, leading to uncontrolled immune activation and hypertension (104,123). The dysregulated BA profile, often with an increased ratio of secondary to primary BAs, can further contribute to inflammation, impair cholesterol homeostasis and, as shown by Nowiński *et al* (98) directly increase cardiac output and blood pressure.

Clinical and preclinical studies support this network view. Patients with acute coronary syndromes or heart failure frequently exhibit this combined metabolomic signature (101,124,125). For instance, Mollar *et al* (126) found that both TMAO and reduced SCFAs levels were associated with small intestinal bacterial overgrowth in patients with decompensated heart failure. In animal models of atherosclerosis, interventions that simultaneously reduce TMAO and increase SCFAs or favorably modulate BAs show superior efficacy compared with targeting a single pathway (127-129). This synergy suggests that the cardiovascular risk attributed to gut dysbiosis is multiplicative rather than additive. The pro-inflammatory state driven by high TMAO and certain BAs is exacerbated by the loss of the anti-inflammatory and homeostatic signals provided by SCFAs. Moreover, TMAO may interfere with BA signaling; studies suggest TMAO indirectly enhances intestinal FXR activity through two main mechanisms: It upregulates hepatic FMO3 to reduce the endogenous FXR antagonist tauro-beta-muricholic acid, and it induces gut dysbiosis that shifts the bile acid pool toward more potent FXR agonists, thereby disrupting a key protective metabolic axis (95,130). Consequently, future diagnostic approaches may benefit from evaluating a panel of gut-derived metabolites rather than a single biomarker, and therapeutic interventions might achieve greater success by employing multi-pronged strategies that rebalance this entire metabolic network to restore cardiometabolic health.

6. Therapeutic horizons and future perspectives

The elucidation of the gut-heart axis has catalyzed a paradigm shift in cardiovascular medicine, moving from purely host-centric pharmacotherapy toward holobiont-targeted interventions. While the association between dysbiosis and CVDs is now well-established, the translation of these findings into clinical practice requires a nuanced transition from broad-spectrum modulation to precision microbiome editing. Current therapeutic strategies are evolving rapidly, focusing on dietary interventions, next-generation probiotics, specific enzymatic inhibition and the integration of multi-omics to address patient heterogeneity (Table III).

Nutritional modulation remains the foundational approach for restoring microbial homeostasis, yet recent evidence suggests that its efficacy is mediated through specific metabolite fluxes rather than generic community shifts. For instance, Gao *et al* (131) demonstrated that the cardiometabolic benefits of the Mediterranean diet are partially driven by the microbial metabolism of BAs, highlighting a specific metabolic conduit linking diet to host health. Similarly, intermittent fasting has emerged as a potent modulator of the gut-heart axis. Yun *et al* (132) reported that intermittent fasting ameliorates resistant hypertension specifically by reshaping the gut microbiota to reduce blood pressure, a finding that aligns with observations by Shi *et al* (133) regarding restructuring the microbiota to lower blood pressure. However, inconsistencies remain regarding the universality of dietary responses. While Madsen *et al* (134) observed favorable shifts in cardiometabolic markers with whole grain consumption in children, Pushpass *et al* (135) noted that while probiotics and fiber sources such as oats altered BA profiles, they did not uniformly translate to improved cardiometabolic risk markers in all subjects. This discrepancy underscores that dietary prescriptions likely require personalization based on an individual's baseline enterotype and metabolic phenotype to be clinically effective.

Beyond dietary modification, the therapeutic landscape is shifting from generic probiotics toward genetically engineered strains and postbiotics. Conventional probiotic supplementation has shown promise, as Spasova *et al* (136) observed notable reductions in TMAO levels in patients with atherosclerosis following *Lactobacillus plantarum* supplementation. Nevertheless, the field is increasingly moving toward 'precision probiotics' designed to perform specific metabolic functions. Chen *et al* (137) developed a nano-functionalized probiotic system that explicitly targets the intestinal TMA-TMAO axis to treat atherosclerosis, demonstrating superior efficacy compared with standard strains. Furthermore, Pham *et al* (83) provided compelling evidence that probiotics engineered to constitutively secrete SCFAs could effectively prevent myocardial injury. This suggests that the future of probiotic therapy lies not in merely replenishing beneficial bacteria, but in delivering bioengineered strains that act as local metabolic factories. Alternatively, the direct administration of postbiotics, such as propionate or butyrate, offers a strategy to bypass the colonization resistance often encountered with live bacteria. Tain *et al* (138) highlighted that reprogramming effects of postbiotic butyrate could avert hypertension programmed by maternal high-fructose diets, suggesting a durable epigenetic impact of these metabolites.

A notable area of therapeutic development involves the non-lethal inhibition of microbial enzymes to reduce toxic metabolites such as TMAO without disrupting the commensal

Table III. Emerging therapeutic strategies targeting the gut-heart axis.

Author, year	Study model	Therapeutic strategy	Specific agent/ intervention	Target mechanism	Key outcome/finding	(Refs.)
Gao *et al*, 2024	RCT	Dietary modulation	Mediterranean diet	Bile acid metabolism	Cardiometabolic benefits are partially mediated by microbial metabolism of bile acids.	(131)
Yun *et al*, 2025	Preclinical	Dietary modulation	Intermittent fasting	Reshaping gut microbiota	Ameliorates resistant hypertension by modulating the microbiota composition.	(132)
Shi *et al*, 2021	Preclinical	Dietary modulation	Intermittent fasting	Microbiota restructuring	Lowered blood pressure through favorable shifts in gut microbial structure.	(133)
Madsen *et al*, 2024	Clinical trial	Dietary modulation	Whole grain intake	Microbiota modulation	Favorable shifts in cardiometabolic markers and gut microbiota in children.	(134)
Pushpass *et al*, 2023	Clinical trial	Dietary modulation	Probiotics, oats, apples	Bile acid profile modulation	Altered bile acid profiles but did not uniformly improve cardiometabolic risk markers.	(135)
Spasova *et al*, 2024	Clinical trial	Probiotics	*Lactobacillus plantarum*	TMAO reduction	Marked reduction in TMAO levels in patients with atherosclerotic cardiovascular disease.	(136)
Chen *et al*, 2025	Preclinical	Precision probiotics	Nano-functionalized probiotic	Inhibiting TMA-TMAO axis	Superior efficacy in treating atherosclerosis compared with standard strains.	(137)
Tain *et al*, 2023	Preclinical	Postbiotics	Butyrate	Epigenetic reprogramming	Reprogramming effects averted hypertension induced by maternal high-fructose diet.	(138)
Tain *et al*, 2023	Preclinical	Enzyme inhibition	Iodomethylcholine	CutC/D inhibition (TMAO)	Inhibited TMAO production and averted programmed hypertension in offspring.	(140)
Ma *et al*, 2022	Preclinical	Natural compounds	Berberine	Downregulating Choline-TMA-TMAO	Treated atherosclerosis via a 'vitamin-like' effect on the microbiota pathway.	(60)
Jiang *et al*, 2024	Preclinical	Natural compounds	Hickory nut polyphenols	Inhibiting TMAO production	Reduced atherosclerosis occurrence by improving microbiota and inhibiting TMAO.	(141)
Yu *et al*, 2025	Preclinical	FMT	FMT	Upregulating GPR43 via propionic acid	Protected against renal ischemia-reperfusion injury.	(142)
Jeong *et al*, 2025	Preclinical	FMT	FMT	Circadian rhythm modulation	FMT failed to impart fasting benefits in stroke models due to circadian dependence.	(143)
Li *et al*, 2025	Preclinical	Sex-specific mechanism	Androgen modulation	Gut microbiota-TMAO pathway	Identified that androgens elevate blood pressure specifically through the TMAO pathway.	(144)
Li *et al*, 2026	Clinical cohort	Multi-omics	Multi-omics integration	Mortality prediction	Integrating multi-omics data notably improved 1-year mortality prediction in heart failure.	(146)

RCT, randomized controlled trial; TMAO, Trimethylamine N-oxide; FMT, fecal microbiota transplantation; CutC/D, choline trimethylamine-lyase.

community structure. Unlike broad-spectrum antibiotics, which Lee *et al* (139) showed can induce a transition from acute kidney injury to chronic kidney disease via dysbiosis, selective inhibitors target specific microbial pathways. Tain *et al* (140) demonstrated that iodomethylcholine effectively inhibits TMAO production and averts programmed hypertension, validating the CutC/D pathway as a druggable target. Concurrently, natural compounds are being re-evaluated for their microbiota-modulating properties. Ma *et al* (60) elucidated that berberine operates via a 'vitamin-like' effect to downregulate the Choline-TMA-TMAO production pathway, a mechanism supported by Jiang *et al* (141) regarding polyphenols. These studies collectively indicate that pharmacological interventions need not be bactericidal but can instead function as metabolic modulators, preserving the ecosystem while silencing pathogenic pathways.

Fecal microbiota transplantation (FMT) represents a more radical intervention for resetting the gut ecosystem, although its application in CVDs is complex and results are occasionally discordant. Yu *et al* (142) found that FMT protected against renal ischemia-reperfusion injury by upregulating GPR43 via propionic acid, suggesting a robust mechanism for systemic protection. By contrast, Jeong *et al* (143) reported a notable limitation where FMT failed to impart the benefits of circadian-dependent intermittent fasting in stroke models. This discrepancy suggests that the 'beneficial' signal of the microbiome is not solely compositional but is also temporally gated by circadian rhythms, implying that the timing of FMT or the rhythmic integrity of the donor sample may be crucial for success in cardiovascular applications. Despite these advances, translational hurdles remain. Inter-individual variability in microbiome responses limits the efficacy of prebiotics and probiotics (82,135). Furthermore, the short half-life of orally administered SCFAs is a major pharmacokinetic barrier, although engineered probiotics secreting SCFAs offer a potential solution (83).

Furthermore, the realization of precision medicine in this field requires addressing demographic variables such as sex and genetics, which have been historically underrepresented. Li *et al* (144) recently identified that androgens elevate blood pressure specifically through the gut microbiota-TMAO pathway, providing a mechanistic basis for the sexual dimorphism seen in hypertension. This finding is complemented by Virwani *et al* (145), who noted distinct sex differences in the association between the gut microbiome and essential hypertension: in males, increased abundance of TMA-producing bacteria (e.g., *Enterobacteriaceae*) correlates strongly with elevated systolic blood pressure and enhanced TMAO generation, whereas in females, higher levels of SCFA-producing commensals (e.g., *Faecalibacterium* and *Roseburia*) exhibit a more pronounced protective effect against hypertension, and overall gut microbial diversity shows a stronger inverse correlation with blood pressure than in males. Consequently, future therapeutic protocols must account for sex-specific microbial interactions. To integrate these complex variables, multi-omics approaches are becoming indispensable. Li *et al* (146) demonstrated that integrating multi-omics data markedly improves mortality prediction in heart failure, while Li *et al* (147) used similar techniques to decode the mechanism of traditional herbal formulas. Therefore, the future of CVDs therapy lies in the convergence of metagenomics, metabolomics and clinical phenotyping to deploy personalized, microbiota-targeted interventions.

Several limitations should be acknowledged. First, most evidence concerning TMAO is observational, and some studies report neutral or context-dependent associations (50,51), highlighting the need for large-scale randomized controlled trials (RCTs). Second, rigorous RCTs for SCFA interventions are lacking. Third, sex differences are underexplored; recent work has shown that androgens increase blood pressure via the TMAO pathway (144), and distinct gut microbiome profiles exist in hypertensive males and females (145). Future studies must incorporate sex as a biological variable.

7. Conclusions

The gut-heart axis is a critical regulator of cardiovascular health, orchestrated by a complex interplay among microbial metabolites. The balance between pro-atherogenic signals such as TMAO and protective molecules such as SCFAs and specific BAs fundamentally shapes cardiovascular risk. A comprehensive understanding of this metabolic network reveals that targeting a single pathway may be insufficient. Future therapeutic strategies should therefore focus on multi-pronged approaches, such as personalized nutrition and precision probiotics, to restore metabolic homeostasis and mitigate cardiovascular disease.

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Authors' contributions

All authors made substantial contributions to this review. MG, ZH, YL, WL and FZ collectively conceived the scope and structure of the review, performed the literature analysis and interpreted the findings. MG and YL drafted the initial manuscript. WL and FZ provided critical revisions for intellectual content. All authors reviewed, edited and approved the final version of the manuscript, and agree to be accountable for the work. Data authentication not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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