doi.org/10.36721/PJPS/2026.40.15921.1

REVIEW

Short-chain fatty acids as precision immunometabolic modulators: Engineering the microbiome for next-generation atherosclerosis therapy

Ming Liu[1#], Ye Chen[2#], Qingru Meng[1] and Zhenrui Tang[3]*

[1]Department of Cardiology, Mudanjiang Cardiovascular Hospital, Mudanjiang 157000, Heilongjiang, China
[2]Department of Geriatric Medicine, Huai'an Hospital of Huai'an City, (Huai'an Clinical Medical College of Jiangsu University), Huaian 223200, Jiangsu, China
[3]Department of Cardiovascular, Thoracic Surgery, Bishan Hospital of Chongqing Medical University, Bishan District People's Hospital, Bishan 402760, China

Abstract: Atherosclerosis is a chronic, low-grade inflammatory process that drives most cardiovascular diseases, beginning with endothelial injury, lipid retention and immune cell infiltration and progressing to plaque formation and rupture. Although current anti-inflammatory therapies, including statins, IL-1β inhibitors and colchicine, have demonstrated cardiovascular benefit, with IL-1β inhibition validating inflammation as a causal target and colchicine exemplifying the potential of repurposed drugs, these approaches remain non-specific and carry systemic side effects. Consequently, there is growing interest in identifying safer and more targeted therapeutic strategies to control vascular inflammation and slow disease progression. This review examines the therapeutic potential of SCFAs in atherosclerosis, focusing on their anti-inflammatory mechanisms, emerging microbiome-engineering strategies and opportunities for precision cardiovascular medicine. A comprehensive literature review was conducted using peer-reviewed articles retrieved from different scientific databases, including Google Scholar, PubMed, Scopus and Web of Science. SCFAs exert broad immunomodulatory and vasculoprotective effects, supporting their therapeutic potential through inhibition of the NLRP3 inflammasome, suppression of NF-κB signaling, promotion of regulatory T-cell differentiation, enhancement of endothelial barrier integrity and stabilization of atherosclerotic plaques. Preclinical studies consistently demonstrate reduced vascular inflammation and attenuation of plaque progression following SCFA-mediated interventions. Emerging biotechnological approaches, including engineered probiotic platforms and gene-editing technologies, enable targeted enhancement of SCFA production and therapeutic efficacy. Furthermore, AI and machine learning tools facilitate the integration of microbiome, metabolomic and clinical datasets to identify responsive patient populations and support the development of personalized synbiotic interventions. SCFAs represent a promising class of microbiome-derived therapeutics that can target key inflammatory pathways involved in atherosclerosis. Combined with advances in microbial engineering and AI-guided precision medicine, SCFA-based interventions may offer a safer and more targeted alternative to conventional systemic anti-inflammatory therapies, supporting their development as next-generation strategies for cardiovascular disease prevention and treatment.

Keywords: Atherosclerosis; Fatty Acids, Volatile; Gastrointestinal Microbiome; Inflammation; Artificial Intelligence

Submitted 29-12-2025 – Revised 01-04-2026 – Accepted 13-04-2026

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INTRODUCTION

Atherosclerosis is now widely recognized as a chronic and progressive inflammatory disease of the arterial wall, leading to a cause of global morbidity and mortality (Bjorkegren and Lusis, 2022). It is the major underlying factor in the development of myocardial infarction, ischemic stroke and peripheral arterial disease and is associated with almost half of all deaths in industrialized societies (Gusev and Sarapultsev, 2023). The initial stage of the disease involves the accumulation of low-density lipoproteins (LDL) and other lipoproteins in the subendothelial tissues, followed by oxidative modification and an inflammatory cascade. Such pathophysiological processes lead to the development of plaque and remodeling of the arterial wall, characteristic of atherosclerotic cardiovascular disease (ASCVD) (Meng *et al*., 2022). Atherosclerotic lesions were first systematically characterized by Ludwig Aschoff. Subsequently, the World Health Organization and the American Heart Association refined these concepts by introducing the notion of complicated plaques and classifying them into clinically relevant categories (Fan and Watanabe, 2022). These plaques are observed in large and medium-sized arteries, especially in regions of low or oscillatory shear stress. One of the major conditions that predisposes the arteries to

**Corresponding author:* e-mail: tzr9419447@outlook.com
#These authors contributed equally and are the co-first authors.

endothelial dysfunction is increased vessel permeability, leading to the influx of modified lipids and immune cells into the inner layers of the arteries. Oxidized LDL (oxLDL) is highly toxic, as it promotes macrophage and T-lymphocyte adhesion and activation, leading to the production of inflammatory cytokines and reactive oxygen species (ROS), which further damage vascular tissue (Blagov *et al*., 2023). Unresolved inflammation and immune dysregulation are major factors that trigger atherosclerosis, promoting the progression of foam cell-rich lesions into fibrous plaques and creating unstable, rupture-prone lesions (Doran, 2022).

Despite the impressive impact of pharmacological therapies in the form of statins, anti-hypertensive agents and anti-platelet agents in relieving the burden of atherosclerotic complications, cardiovascular disease (CVD) remain the leading cause of mortality worldwide. It is expected to cause about 23 million deaths annually in 2030 (Buja, 2023). Given this persistent global burden, the gut microbiota is a promising area of research because it is vital to host metabolism, immune homeostasis and vascular homeostasis. Short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate are also among the major microbial metabolites that modulate cardiovascular health (Alexandrescu *et al*., 2024).

The intestinal microbiota modulates multiple facets of cholesterol metabolism and critical metabolic pathways that influence oxidative stress and inflammation processes, including key signaling axes such as NF-κB and the NLRP3 inflammasome, which play central roles in endothelial activation and vascular inflammation in atherosclerosis (Rauf *et al*., 2022). Beyond inflammatory signaling, atherosclerosis also involves mitochondrial dysfunction, impaired lipid trafficking that promotes foam cell formation and complex interactions—such as cytokine-mediated activation—between endothelial cells and immune mediators within the vascular microenvironment (Libby and Soehnlein, 2025). Together, these interconnected mechanisms contribute to plaque initiation and progression.

Furthermore, several gut microbiota metabolites, such as various bile acids, lipopolysaccharides and trimethylamine-N-oxide, influence these pathways and states (Yao *et al*., 2022). The therapeutic uses of SCFAs are among the few examples of microbial metabolites that play an important role in maintaining gut health. SCFAs have anti-inflammatory effects that prevent the release of specific pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1β and activate Tregs to sustain immune homeostasis (Bui *et al*., 2025). These immunological actions of SCFAs are crucial for promoting cardiovascular health. It also lowers circulating LDL and cholesterol levels, which, in turn, improves vascular function and elasticity (Nogal *et al*., 2021).

Moreover, mechanistically, SCFAs have been reported to suppress histone deacetylase (HDAC) expression, modulate MAPK and renin-angiotensin signaling pathways and enhance endothelial nitric oxide availability, all of which contribute to reduced atherosclerotic progression (Wang *et al*., 2025). While preclinical studies in animal models have provided compelling evidence of the cardiovascular benefits of SCFAs, the translation of these findings to humans remains complex and requires careful consideration. The interindividual variability in gut microbiome structure also challenges its application in humans, as it may affect SCFA production and efficacy. Moreover, SCFAs may exert off-target metabolic effects, potentially affecting pathways beyond the intended cardiovascular targets, which were not fully captured in animal models. These limitations underscore the need for strategies that can reliably modulate SCFA production and function in a safe and individualized manner (Edpuganti *et al*., 2025).

These challenges further emphasize the need for advanced strategies, such as next-generation probiotics (NGPs), microbiome engineering and personalized SCFA-targeted therapies, to bridge the gap between preclinical promise and clinical applicability in cardiovascular disease management. NGPs are engineered microbial therapies that target disease pathways in the gut microbiome, unlike traditional probiotics, which provide general support to gut health. Researchers are designing NGPs to specifically modulate gut microbial functions and produce therapeutic metabolites (Gill *et al*., 2018). In contrast, innovative synthetic biology, microbiome engineering and CRISPR/Cas9 gene editing are being used to develop these precision probiotics. For example, microbial SCFA over-producers, SCFA-secreting bioactive peptide producers and gut inflammation-responsive engineered microbes are designed (Facchin *et al*., 2024). Genetic engineering is being pursued using published microbial chassis, including *E. coli*, *Lactobacillus*, *Bifidobacterium* and *Clostridium butyricum*. Surface encapsulation with various polysaccharides and silk fibroin is designed to increase engineered microbe colonization and survivability in the gastrointestinal tract (Li *et al*., 2024).

CRISPR/Cas9 technology is an innovation in enhancing the functionality of probiotics. Stress-resistance SCFA biosynthesis genes or genes with anti-inflammatory properties may be inserted or up-regulated for therapeutic improvement (Asif *et al*., 2024). In cardiovascular cases, improved SCFAs produced by maintained gut delivery may enhance endothelial function, reduce systemic inflammation and alter lipid metabolism. In addition, new and modified metabolic pathways are introduced to expand probiotics' dietary substrate utilization and increase the production of cardio-protective metabolites (Kantor *et al*., 2025). The development of therapeutics aimed at understanding SCFAs has been facilitated by their

increasing availability and the unprecedented application of machine learning. AI models utilize large-scale multi-omics data, including genomics, metabolomics, microbiomics and clinical data, along with other records, to determine which microbial strains or consortia enhance SCFA production, modulate the immune system and are safe when used with SCFA-interacting medications (Al-Adham *et al*., 2025). Innovative gut ecosystem simulators, along with artificial neural networks, can categorize and rank probiotic candidates based on their functional genetic attributes (Lv *et al*., 2024). These tools use predictive modeling of interventions on SCFA to provide individually customized recommendations based on personalized medication, microbiome and cardiovascular risk profile (Ai, 2021; Tiwari *et al*., 2024).

This review will discuss how SCFAs regulate atherosclerosis and vascular inflammation and how their clinical utility can be enhanced through advanced biotechnological devices. Moreover, it will describe the primary opportunities and obstacles in developing SCFA-based approaches into novel athero-therapeutic tools for atherosclerotic cardiovascular disease.

Development of atherosclerosis: Pathophysiology and progression

Atherosclerosis begins with endothelial dysfunction, which allows LDL to infiltrate and oxidize within the arterial wall. This leads to inflammation, the recruitment of monocytes, the development of foam cells and early fatty streaks (Tonch-Cerbu *et al*., 2025). Continued immune system activation and smooth muscle cell proliferation will yield a fibrous plaque. The rupture of plaque can lead to thrombosis and such consequences as myocardial infarction or stroke can occur, which is a more progressive disease (Fernando *et al*., 2020).

Endothelial dysfunction: The initial trigger

Atherosclerosis initiates with endothelial dysfunction. In this context, the term 'dysfunction' refers to the endothelial lining of blood vessels losing its regulatory control. The endothelium can prevent vasculature/innate inflammation and clot formation through the production of nitric oxide (NO) (Tasouli-Drakou *et al*., 2025). Under the influence of risk factors like hypertension, high cholesterol, diabetes, tobacco use and oxidative stress, no production becomes deficient and a vascular imbalance is brought about. The endothelium synthesizes nitric oxide, which prevents the vascular system from thrombosis and vascular inflammation. This impaired production of NO eventually leads to dysfunction and imbalance of the vascular system. This type of dysfunction initiates a cascade of pathological events (Popa-Fotea *et al*., 2023). Furthermore, injured endothelial cells begin to express adhesion molecules, such as VCAM-1 and ICAM-1, which enhance monocyte adhesion and transmigration into the intimal layer of the blood vessel. The intimal monocytes differentiate into macrophages, which take up oxidized LDL and form foam cells, which promote the development of atherosclerotic plaques (Fig. 1) (Ministrini *et al*., 2021).

Oxidative stress can significantly predispose to endothelial dysfunction, as NO is depleted and LDL is oxidized. Besides this, the inflammatory process can also be triggered by the endothelial cells producing pro-inflammatory cytokines (eg, TNF-α and IL-6) (Kowara *et al*., 2021). The endothelium may also change from an anticoagulatory to a procoagulatory state, thereby contributing to increased clotting, particularly when the plaque ruptures. This can lead to severe outcomes like thrombotic heart disease and other cardiovascular events like ischemic strokes (Jiang *et al*., 2022).

Lipid accumulation and foam cell formation

After LDL is trapped and modified in the arterial wall, the oxidized and modified LDL preferentially invades monocytes in the blood flow to the intima (Fig. 1). These monocytes differentiate into macrophages. These specialized immune cells play a crucial role in eliminating foreign particles and dead cells (Frąk *et al*., 2022). Macrophages that internalize the oxLDL particles by their scavenger receptors, like CD36, are overloaded with lipids and are transformed into foam cells. Foam cells, so-called from their microscopic appearance, increase in the plaque and become a hallmark of fatty streaks (Botts *et al*., 2021). This lipid deposition also plays a role in plaque inflammation, as foam cells release pro-inflammatory cytokines, including TNF-alpha, IL-1 beta and IL-6, which recruit more leukocytes, perpetuating the inflammatory spiral. Also, foam cells undergo an apoptotic process and a necrotic core forms, which is one of the main features of susceptible plaques (Kong *et al*., 2022).

Immune cell infiltration and inflammation

After endothelial dysfunction, infiltrating immune cells and inflammation primarily regulate the onset and progression of atherosclerosis. It is the damaged endothelium that activates adhesion molecules, such as VCAM-1 and ICAM-1, which promote the circulation of monocytes and T cells in the lesion (Ye *et al*., 2022). After entering the arterial wall, monocytes differentiate into macrophages and phagocytose oxidized low-density lipoprotein (oxLDL), which eventually transform into foam cells. The foam cells confluence consists of a fatty streak, the earliest lesion that is observed in atherosclerosis (Fig. 1). Moreover, macrophages produce pro-inflammatory cytokines in response to these agents namely IL-1b, TNF-a and IL-6, which subsequently enhances inflammatory responses and increases the influx of immune cells, creating a vicious cycle of inflammatory response (Xia *et al*., 2023).

Furthermore, T lymphocytes are another key factor that contributes to the proinflammatory milieu, releasing IFN-γ, which stimulates macrophages and results in inflammation mainly of the Th1 subtype. Dendritic cells

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and mast cells infiltrating the atherosclerotic plaques contribute to the immunological intricacy. As plaque inflammation and immune cell content increase, plaque stability decreases. Macrophage-released matrix metalloproteinases (MMPs) significantly degrade the fibrous cap, thereby increasing the risk of its rupture, which in turn increases the risk of thrombosis and promotes cell death (Ye *et al*., 2022).

Smooth muscle cell migration and fibrous cap formation

Vascular smooth muscle cells (VSMCs) play a role in the pathogenesis and stability of atherosclerotic plaques. VSMCs located in the arterial media respond to both inflammatory and injury signals and switch their phenotype to a synthetic one. Consequently, they are able to enter the intima, proliferate and produce ECM proteins, including collagen and elastin (Grootaert and Bennett, 2021). These ECM proteins are constituents of the fibrous protective cap that encases the lipid-rich center of a plaque, as shown in Fig. 1. Stabilization of the plaque and minimization of rupture are achieved through thick, collagen-rich fibrous caps, as opposed to thin caps, which are susceptible to rupture, MMPs and thrombotic phenomena (Chen *et al*., 2023). Furthermore, VSMCs' ECM production, lipid accumulation, inflammatory signaling and the ECM matrix formed are provocative in plaque formation and inflammatory signaling. Within these boundaries, VSMCs stabilize the plaque by forming fibrous caps and, simultaneously, modify the destabilizing conditions that contribute to plaque progression (Yu *et al*., 2024).

Chronic inflammation and plaque progression

This chronic inflammation, as well as lipid deposition, also contributes to the further development of plaque in the process of atherogenesis. Infiltrative immunological plaque cells release pro-inflammatory cytokines IL-1, TNF-2 and IL-6.. IL-1β and TNF-α further increase inflammation by stimulating the NF-κB, JAK-STAT pathways and then induce the synthesis of adhesion molecules, chemokines and other inflammatory cytokines. This inflammatory cytokine network, by persistent activation, drives the rapid expansion of atheromatous plaques and increases their instability (Fig. 1) (Miao *et al*., 2023).

Additionally, oxidative stress plays a key role in atherosclerosis. However, ROS damage activated macrophages and other immune cells in the plaque, attracting additional immune cells, worsening the proinflammatory environment. Inflammatory stress, macrophage destruction and lipid peroxidation products further promote atherosclerosis by modifying LDL and forming foam cells (Gurgoglione *et al*., 2023).

Traditional therapeutic strategies for atherosclerosis

Statins are also useful for inhibiting the enzyme HMG-CoA reductase, thereby decreasing cholesterol synthesis and the expression of LDL receptors in the liver. This, in turn, lowers circulating LDL-C concentrations and has anti-inflammatory effects. Table 1 indicates that statins inhibit the synthesis of C-reactive protein, activate endothelial nitric oxide synthase (eNOS) and reduce the expression of adhesion molecules on the vascular endothelium (Narkhede *et al*., 2024). These effects vary in terms of magnitude depending on the statin class and dosage. For example, 40 mg/day Simvastatin has a pronounced effect on reducing CRP and 80 mg/day Atorvastatin has long-term advantages.

The PRINCE trial showed that pravastatin reduces CRP regardless of LDL-C and the HOPE-3 trial demonstrated the same with rosuvastatin in the intermediate-risk group. Massive studies, including PROVE-IT, TIMI 22 and JUPITER, are additional proof of the dual lipid-lowering and anti-inflammatory effects of high-intensity statins. Nevertheless, inflammatory risk persists in most patients despite statin use, indicating that the inflammatory component of atherosclerosis cannot be completely suppressed by statins (Zhang *et al*., 2022).

The CANTOS trial showed that reducing cardiovascular events could be achieved by targeting inflammation, regardless of cholesterol levels (Table 1). Canakinumab, an IL-1β inhibitor, reduced recurrent events by 15% in post-MI patients with elevated CRP, without altering lipid levels. The greatest benefits were observed in those with the largest CRP reductions, supporting the use of inflammatory biomarkers to guide therapy. However, canakinumab use is limited by increased infection risk and high cost, raising concerns about long-term safety and feasibility in broader populations (Kim and Jang, 2024).

Furthermore, the anti-inflammatory effect of colchicine, mainly mediated by inhibition of the NLRP3 inflammasome and the prevention of pro-inflammatory cytokine production, has become a promising treatment agent in atherosclerosis (Table 1). Its advantages include oral administration, affordability and the potential to reduce residual inflammatory risk in patients with cardiovascular disease. It is, however, clinically limited by its gastrointestinal side effects and drug interactions, especially with statins. Although it shows a slight decrease in cardiovascular events, long-term adherence might be influenced by tolerability, which can affect overall effectiveness in regular clinical practice (Gonzalez *et al*., 2022).

SCFAs in immunometabolic reprogramming and vascular homeostasis

More than 100 trillion microorganisms live in the gastrointestinal tract of adults, with most of them controlling host physiology by producing microbial metabolites such as short-chain fatty acids (SCFAs). These SCFAs were traditionally considered mere simple sources of energy but have lately been considered key regulators of host immunity, metabolism and vascular activity. (Zhang *et al*., 2021).

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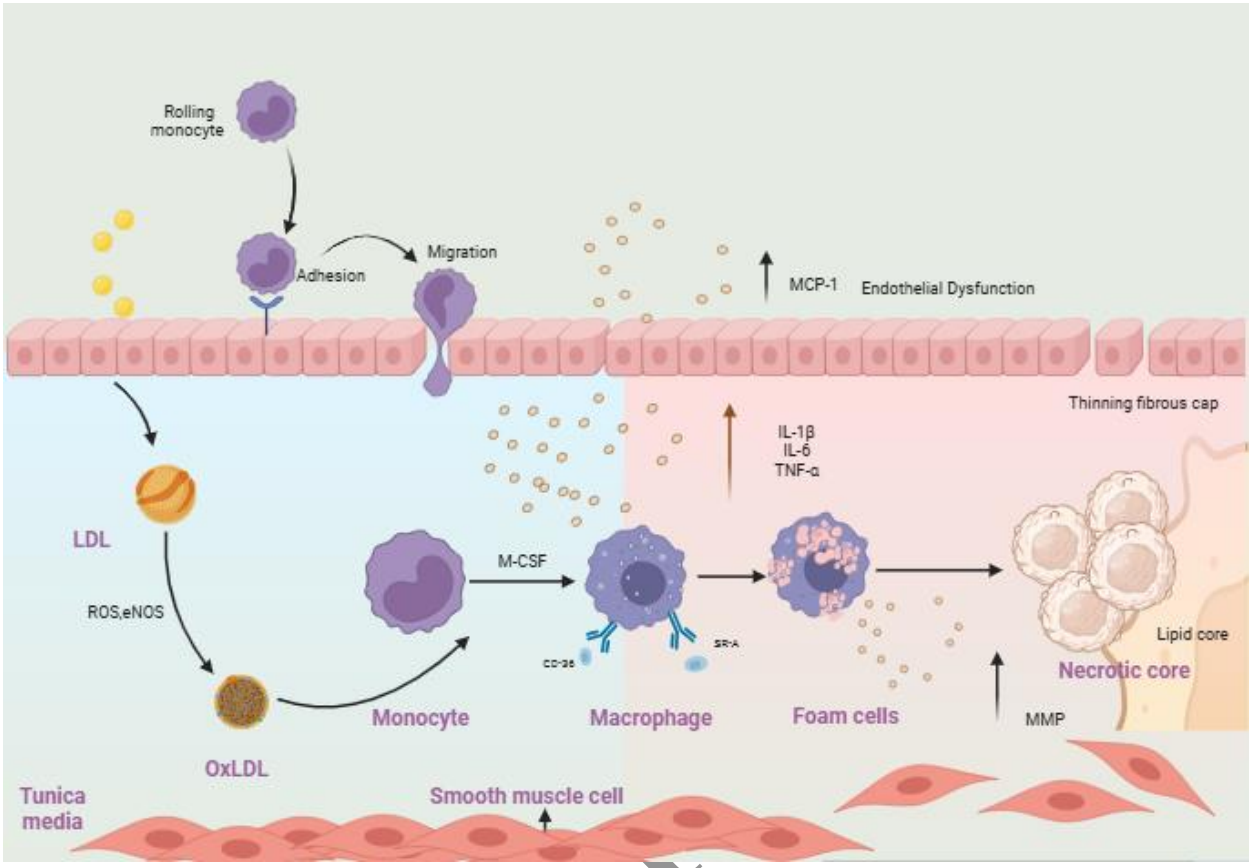

Fig. 1: Development of atherosclerosis: Pathophysiology and progression: Atherosclerosis starts with LDL oxidation by ROS, forming oxLDL. Monocytes move across broken endothelium where they differentiate to become macrophages that ingest oxLDL to form foam cells. This activates proliferation of smooth muscle cell, inflammation, and necrotic centres. In developed plaques, calcification has an influence on stability.

Molecular mechanisms of SCFA action: Receptors and epigenetic modulation

G-protein coupled receptors (GPCRs)

SCFAs are endogenous ligands of G protein-coupled receptors, which are nutrient-sensing, such as GPR41 (FFAR3), GPR43 (FFAR2) and GPR109A (HCAR2). The binding of SCFAs to these receptors controls a wide range of physiological activities, most of which do not involve only the gastrointestinal system (Table 1) (Liu *et al*., 2025). GPR41 is mostly stimulated by propionate, where acetate, butyrate and pentanoate are also active. It shows widespread tissue expression, with much greater expression in adipose tissue, arterial and arteriolar endothelium, brain endothelial cells, peripheral vasculature and cortical neurons. GPR41 interacts with Galpha i/o, which activates phospholipase C, elevates intracellular calcium, phosphorylates Erk1/2 and decreases cAMP, thereby regulating vascular tone, epithelial barrier function, immune responses and energy homeostasis (Chulenbayeva *et al*., 2025).

GPR43 is primarily activated by propionate and acetate, with butyrate being less effective. Initially, GPR43 was indentified in the intestinal mucosa, peripheral vasculature, brain, heart, adipose tissue, kidney and liver (Zhang *et al*., 2024). GPR43 couples to both Gαi/o and Gαq proteins and interacts with β-arrestin-2, which modulates receptor internalization and desensitization. Through this signalling it mediates SCFA effects on immunity, intestinal homeostasis, gut hormone synthesis, vascular tone, insulin and leptin production and anti-inflammatory actions in microglia and macrophages (Sun *et al*., 2026).

GPR109A, originally known as the niacin receptor, has high affinity for niacin and 3-hydroxybutyrate, while butyrate is a low-affinity agonist and propionate and acetate do not activate it. It is expressed in intestinal and mammary epithelia, immune cells, adipocytes and the brain, with intestinal expression dependent on the gut microbiota (Feng *et al*., 2026). GPR109A couples to Gi/Go proteins and recruits β-arrestins to the cell membrane. Activation of this receptor helps maintain intestinal barrier integrity, alleviates oxidative stress and inflammation, enhances tight-junction protein expression and may contribute to blood–brain barrier regulation as shown in animal models (Dicks *et al*., 2024).

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Table 2: Comparative analysis of existing anti-inflammatory therapies in atherosclerosis.

Sr. No.	Therapy	Source of therapy	Mechanism of action	Observed effects	Limitations	References
1	Statins	Synthetic drugs (e.g., atorvastatin, simvastatin)	Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis and associated inflammation, particularly in cardiovascular diseases.	Significant reduction in LDL cholesterol, improved endothelial function, reduced cardiovascular risk, and long-term heart health.	Side effects such as muscle pain, liver damage, and risk of diabetes.	Sinha *et al*., 2024
2	PCSK9 Inhibitors	Monoclonal antibodies (e.g., evolocumab, alirocumab)	PCSK9 inhibitors prevent the degradation of LDL receptors, increasing LDL cholesterol clearance, reducing atherosclerotic inflammation.	Dramatic reduction in LDL cholesterol, stabilization of atherosclerotic plaques, and lower incidence of heart attacks.	High cost, subcutaneous injection, and uncertain long-term safety data.	Hedin *et al*., 2019
3	IL-1β Blockers	Monoclonal antibodies (e.g., anakinra, canakinumab)	IL-1β blockers inhibit interleukin-1β, a key pro-inflammatory cytokine, reducing systemic inflammation in autoimmune diseases.	Reduction in inflammation, alleviation of joint pain, and improvement in mobility and function in diseases like rheumatoid arthritis.	Increased risk of infections due to immune suppression and higher treatment costs.	Yu *et al*., 2024
4	Colchicine	Naturally derived (from the *Colchicum autumnale* plant)	Colchicine inhibits microtubule polymerization, reducing neutrophil migration and cytokine release, thus reducing inflammation.	Reduction in acute gout flare-ups, less joint pain and swelling, and improved long-term management of gout.	Gastrointestinal side effects (nausea, diarrhea), and toxicity at high doses.	Zhang *et al*., 2021

Epigenetic regulation via HDAC inhibition

Amongst all epigenetic modifications, histone acetylation has been most thoroughly studied. Histone acetylation is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Mirzaei *et al*., 2021). HDAC activity compacts chromatin and suppresses transcription, while HDAC inhibition relaxes chromatin and promotes gene expression. This also affects many non-histone proteins. In the cardiovascular system, altered HDAC expression and histone hypoacetylation have been linked to cardiac injury, vascular dysfunction and maladaptive remodeling (Xie *et al*., 2023). Specific HDAC inhibitors (e.g., HDAC3 or HDAC9) have also been shown to decrease inflammation, oxidative stress and endothelial dysfunction and to maintain the integrity of vascular and cardiac tissues (Zhang *et al*., 2021).

Short-chain fatty acids (SCFAs) act as natural HDAC inhibitors. Butyrate is the most potent, followed by propionate and pentanoate and SCFAs can also lower HDAC expression (Fig. 2). Their inhibitory effect occurs directly, after entering cells and indirectly through activation of GPR41, GPR43 and GPR109A receptors (Swaroop *et al*., 2021). In endothelial and cardiac cells, these dual actions modulate inflammatory signalling, enhance tight-junction and barrier proteins and support vascular tone. Together, SCFA-induced HDAC inhibition and receptor-mediated signaling contribute to cardioprotective effects, making SCFAs important mediators at the interface of metabolism, epigenetic regulation and heart health (Song *et al*., 2022).

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Table 2: Summary of short-chain fatty acids (SCFAs) and their molecular targets.

Sr. No.	SCFA	Primary GPCR targets	Epigenetic targets (HDAC Inhibition)	Key molecular mechanisms	Vascular & immune effects	References
1	Acetate	GPR43 > GPR41 (low affinity for GPR109A)	Mild inhibition of HDAC1/2	Activates G α i/o and G α q signaling via GPR43 → ↓ cAMP, ↑ Ca^{2+}, ERK1/2 activation	- Improves endothelial barrier function- Reduces systemic inflammation- Modulates lipid metabolism	(Chun and Toldi, 2022)
2	Propionate	GPR43 = GPR41 >> GPR109A (inactive)	Moderate inhibition of HDAC1/2/3	Enhances β-arrestin signaling, modulates Foxp3+ Treg induction, suppresses NF-κB activation	- Enhances Treg proliferation- Suppresses VCAM-1 and IL-6/IL-8 expression- Regulates macrophage lipid handling	(Aragam and Natarajan, 2020)
3	Butyrate	GPR109A >> GPR43 > GPR41	Strong inhibition of HDAC1/2/3/8	Alters chromatin acetylation (Foxp3 locus), blocks NF-κB p65 nuclear translocation, activates Nrf2 via AHR/P300	- Inhibits monocyte/macrophage migration- Prevents foam cell formation- Suppresses VSMC proliferation- Enhances antioxidant gene expression via Nrf2	(Chang *et al*., 2024)

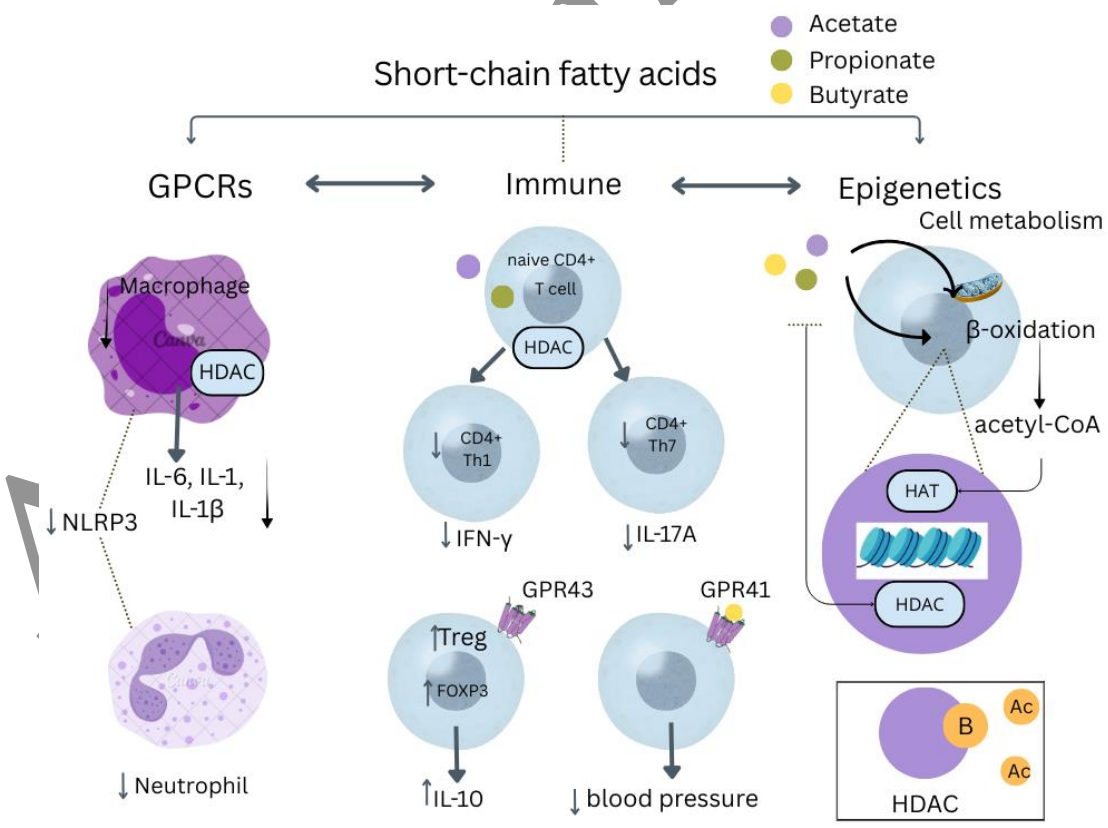

Fig. 1: Molecular mechanisms of action of short-chain fatty acids (SCFAs) and their potential role in lowering blood pressure (Chang *et al*., 2024).

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SCFAs improve endothelial cell inflammation and oxidative stress

SCFAs regulate inflammatory and oxidative stress pathways, including NF-KB and Nrf2, thereby reducing endothelial damage and delaying the onset of atherosclerosis (Medina-Leyte *et al*., 2021). Under physiological conditions, NF-κB is a key protein complex involved in inflammation, remaining inactive in the cytoplasm under normal conditions due to its association with the inhibitory protein IκB (Mansuy-Aubert and Ravussin, 2023). Stimulation of IκB by oxLDL and other pro-inflammatory agents leads to endothelial cell dysfunction through the expression of pro-inflammatory genes (He *et al*., 2020).

Shi *et al*. (2025) reported that butyrate decreased p65 concentration in the endothelial cell and its translocation into the cell nucleus, thus preventing the formation of p65/p50 heterodimers. Meanwhile, it also increased p50 concentration in the cytoplasm. This increase in cytoplasmic p50 is advantageous in inhibiting the formation of p50/p50 homodimers and hence suppresses the activation of NF- 0 b genes. Additionally, NF-κB transcriptional activity is regulated by acetylation and deacetylation of proteins in the NF-κB pathway, as well as by the availability of NF-κB target genes. For example, NF-κB (p65 and p50) subunits can interact with HDAC to suppress transcription.

The second important pathway that SCFAs control is the Nrf2 transcription factor in response to cellular oxidative stress. A study using an Nrf2 knockout diabetic mouse model revealed that butyrate significantly decreased the concentrations of various adhesion molecules and reactive oxygen species (ROS). Nonetheless, this protective outcome was nullified in Nrf2-deficient mice, validating the idea that SCFAs' positive effects on endothelial inflammation and oxidative stress are, in large part, mediated by Nrf2 activation. The SCFAs prevent HDACs, thereby inducing the recruitment of AHR and P300 coactivators to the Nrf2 gene promoter, which enhances Nrf2 expression. After activation, Nrf2 translocates to the nucleus, where it interacts with antioxidant response elements (ARE), decreases ROS levels and enhances redox homeostasis in endothelial cells (Fig. 2).

Furthermore, compared with conventional anti-inflammatory therapies, SCFA-mediated regulation exhibits a broader, multi-targeted mechanism. IL-1β blockers, such as canakinumab, provide high specificity for a single pro-inflammatory cytokine, effectively reducing systemic inflammation but increasing the risk of immunosuppression and infections (Alfaddagh *et al*., 2020). Colchicine, a microtubule polymerization inhibitor, suppresses neutrophil activity and inflammasome activation, yet carries dose-dependent gastrointestinal and cytotoxic side effects (Feng *et al*., 2025).

In contrast, SCFAs naturally modulate multiple interconnected pathways—NF-κB, Nrf2 and potentially the NLRP3 inflammasome—through endogenous epigenetic and transcriptional mechanisms, offering a safer profile with a lower risk of off-target immunosuppression (Lu *et al*., 2022). Although quantitative comparisons remain limited, preclinical studies indicate that SCFAs can exert significant anti-inflammatory and vascular-protective effects, potentially complementing pharmacologic agents or serving as an adjunctive therapy in cardiovascular disease management (Jin *et al*., 2022).

SCFAs inhibit the migration of monocytes/macrophages

When the vascular endothelium is damaged, blood monocytes cross the endothelium, enter the subendothelial space and trigger atherosclerosis. Monocyte recruitment, adhesive interactions, chemokines and enzyme cascades drive this process by allowing monocytes to contact, adhere and migrate through the endothelium (Bartolomaeus *et al*., 2019). Butyrate reduces atherosclerotic lesions by lowering MMP-2 and VCAM-1 levels, thereby decreasing monocyte adhesion and migration into lesions, particularly in aortic atherosclerosis (Table 3) (Kumar, 2025). In vitro studies show that short-chain fatty acids (SCFAs) suppress the production of pro-inflammatory cytokines IL-6 and IL-8 and reduce VCAM-1 expression and monocyte adhesion to human umbilical vein endothelial cells (HUVECs). SCFAs therefore mitigate lesion inflammation and reduce monocyte attraction to the inflamed endothelium (Wang *et al*., 2025).

Moreover, the iNOS/Src/FAK pathway is crucial for macrophage motility activated by Toll-like receptors (Zhang *et al*., 2025). Src and Focal Adhesion Kinase (FAK) are central to the processes of cell adhesion and movement. Sayols-Baixeras *et al*. (2023) showed that butyrate prevents migration of LPS-activated RAW264.7 macrophages from the peritoneal cavity. This is consistent with the description of iNOS as an activator of Src regarding mobile macrophages. After LPS-activated butyrate-pretreated macrophages, inactivation of iNOS and Src, as well as control mechanisms with Src and FAK, were thought to explain butyrate's effect on the LPS-activated motility of macrophages by disabling the iNOS/Src/FAK pathway and reducing their movement toward the lesion. Butyrate's control action is corroborated by the imposition of iNOS, atypical NOX and ROS, along with superoxide, active macrophage targets supporting lesion-policing macrophage motility.

SCFAs regulate lipid metabolism of macrophages

Once macrophages internalize cholesterol esters, the esters are processed within lysosomes. Subsequently, macrophages degrade the esters and transfer the resulting cholesterol out of the cell using ATP-binding cassette

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transporters: ABCA1 (ATP-binding cassette transporter A1) and ABCG1 (ATP-binding cassette subfamily G member 1), thereby facilitating cholesterol release (Sukhorukov *et al*., 2020). Butyrate intrinsically stimulates this process by activating the PI3K signaling pathway, leading to the phosphorylation of the transcription factor Sp1. Phosphorylated Sp1 then binds to the ABCA1 promoter to enhance ABCA1 gene transcription and promote cholesterol efflux (Laguna-Maldonado *et al*., 2025). Furthermore, butyrate regulates this mechanism via the short-chain fatty acid (SCFA) receptor GPR109A; its stimulation augments ABCA1 expression in macrophages. This pathway, which may involve downstream targets such as Apollo-1, also promotes cholesterol efflux. Collectively, these mechanisms upregulate ABCA1 and enhance cholesterol efflux in macrophages, thus preventing foam cell formation—a critical step in atherosclerosis development (Panyod *et al*., 2023).

SCFAs regulate proliferation and migration of smooth muscle cells

Vascular smooth muscle cells (VSMCs) undergo structural and functional changes closely linked to atherosclerosis, which allows plaque formation and instability (Guo *et al*., 2025). Studies show that butyrate efficiently inhibits VSMC proliferation, arterial wall thickening and collagen deposition. Butyrate's protective mechanism maintains specific histone modifications in VSMCs (Han *et al*., 2026). For example, butyrate treatment alters histone H3 at specific genomic sites in VSMCs. These changes affect chromatin structure to selectively enhance negative regulators and suppress positive regulators of the cell cycle. This targeted regulation leads to the arrest of VSMC proliferation (Zhang and Gerard, 2022).

Gerhardt *et al*. (2022) demonstrated that colonizing germ-free ApoE−/− mice with butyrate-producing *Roseburia intestinalis* exerts atheroprotective effects by enhancing intestinal barrier integrity and reducing circulating endotoxin levels. This improvement in gut barrier function was associated with decreased expression of pro-inflammatory mediators, including Tnf-α and Vcam1 in the aortic wall. Colonized mice develop smaller atherosclerotic lesions, less macrophage infiltration and plaques with more collagen, reflecting increased stability. These findings suggest SCFA-generating microbes reduce systemic inflammation and directly stabilize atherosclerotic plaques, highlighting the therapeutic potential of targeting the gut-heart axis in cardiovascular disease.

SCFAs promote proliferation and differentiation of Treg cells

Microbial metabolites regulate the immune system by controlling regulatory T (Treg) cell development and activity. Treg cells play a crucial role in the pathogenesis of atherosclerosis, which involves immune tolerance (Du *et al*., 2022). Moreover, short-chain fatty acids (SCFAs) promote Treg cell growth and differentiation through multiple mechanisms. For example, the inhibition of histone deacetylases (HDACs) is a major pathway that leads to increased histone acetylation and positive gene expression. This, in turn, enhances Foxp3 expression, a transcription factor essential for Treg identity and function. Some SCFAs are especially potent HDAC inhibitors, efficiently increasing Treg populations (Hu *et al*., 2022).

In addition, activation of receptors such as GPR43 and GPR109A stimulates anti-inflammatory pathways and supports the development of regulatory T (Treg) cells, which maintain immune tolerance by suppressing excessive immune responses (Liu *et al*., 2023). SCFAs also stimulate the production of key anti-inflammatory cytokines, such as IL-10 and TGF-β, necessary for Treg stability and function. These immunoregulatory actions significantly impact atherosclerosis, a chronic inflammatory arterial wall disease (Lu *et al*., 2022). SCFAs enhance Treg-mediated immune control, inhibit the formation of atherosclerotic plaques, reduce vascular inflammation and promote endothelial integrity (Chang *et al*., 2024).

SCFAs in Gut–Organ Axes and Cardiovascular Health

Recently, more attention has focused on the role of SCFAs in maintaining the body's balance. Their effects go beyond the gut to reach other parts of the body—like the brain, kidneys, liver, lungs, bones and heart—through pathways known as the "gut–organ axes" (Gao et al., 2024). SCFAs, which are the main products of gut bacteria, act as signals by binding to specific cell receptors (like GPR41 and GPR43) and blocking histone deacetylases. This controls which genes are active and how immune cells work. In this way, SCFAs help the gut "talk" to distant organs and manage normal and disease processes throughout the body. This new understanding explains how metabolites from the microbiota contribute to disease development and may guide new approaches to diagnose and treat illness (Yukino-Iwashita *et al*., 2022).

Therefore, therapeutic strategies that target the gut–heart link—such as changing diets, adding beneficial bacteria and using fecal microbiota transplants—aim to restore bacteria that produce SCFAs, boost SCFA levels and strengthen the gut barrier. These actions help protect the heart. Together, these results show the gut is key in regulating heart health, with SCFAs as important messengers between the gut and heart. This opens up new ways to use the microbiome to treat heart dysfunction (Table. 3) (Fusco *et al*., 2023).

SCFAs in the context of next-generation therapeutics

Novel therapeutic probiotics (NGPs) represent a significant area of innovation in medical research, advancing the development of more effective, targeted probiotics. They

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are high-tech probiotics that selectively perform specific therapeutic tasks by regulating the gut microbiome, complementing the action of regular probiotics and providing novel approaches to chronic disease treatment (Fakruddina *et al*., 2022). (Nandal *et al*., 2025). Unlike pharmaceutical agents (e.g., statins) that carry side effects (e.g., myopathy), probiotics are generally safe and exert pleiotropic effects, including cholesterol-lowering, anti-inflammation and endothelial protection (Ahmed *et al*., 2024).

Hassan *et al*. (2024) reported that supplementation with a specific Lactobacillus plantarum strain in atherosclerosis-prone mice reduced markers of cell damage and inflammation. Recently, O'Morain *et al*. (2021) showed that giving a group of beneficial bacteria (Lab4P) along with a high-fat diet to mice lacking LDL receptors led to less buildup of fatty and immune cells in the arteries. This also increased the presence of muscle-like cells in these plaques. These findings suggest more stable arterial walls and healthier blood lipid levels.

The role of probiotics appears significant in supporting gut microbiome balance and reducing TMAO production. It has also been demonstrated that mice fed a high-choline diet and given Bifidobacterium animalis had reduced TMAO levels and better lipid metabolism compared to those with atherosclerosis (Alenazy *et al*., 2022). Interestingly, along with probiotics, synbiotics—a combination of probiotics (beneficial live microorganisms) and prebiotics (non-digestible food components that selectively stimulate these probiotics)—have been considered a potential biotherapy for managing atherosclerotic risk factors such as hypercholesterolemia and hyperlipidemia (Bhatia *et al*., 2025). Synbiotics have been reported to have an additive effect, as they not only restore normal microbiota by stimulating the proliferation of beneficial bacteria, but also modulate lipid metabolism and cholesterol levels. Researchers have demonstrated that synbiotics containing L. casei, maltodextrin and fructooligosaccharide as positively influenced cholesterol levels and the gut microbiome, without causing translocation of lactobacilli to other organs (Olas, 2020).

Examining the role of synthetic biology

Synthetic biology enables intermediate-level modifications of probiotics, transforming them into targeted, intelligent therapeutics that can deliver more controlled therapies by monitoring and responding to host cues (Deehan *et al*., 2020; Patterson *et al*., 2017). It is also important to choose which chassis-engineerable probiotic strains will be used. The microbial chassis used in the engineering of probiotics must be affordable, flexible enough and simple to colonize by the required microorganisms. The most widespread ones are *E. coli*, *Lactobacillus*, *Bifidobacterium*, *Bacteroides*, *Clostridium butyricum* and *Saccharomyces boulardii* (Li *et al*., 2024). Each of them has its advantages and challenges. In addition, engineered probiotics must be successfully colonized. Some of them, including surface modification, could enhance survival and adhesion of the gastrointestinal tract. Genetic modification and competitive niche have also been used to do it (Yang *et al*., 2024; Shen *et al*., 2021).

Utilizing CRISPR/Cas9 gene editing

In recent years, innovations in gene editing have revolutionized molecular biology, with the CRISPR/Cas9 system emerging as a particularly transformative tool (Hu *et al*., 2018). Beyond its widespread applications in mammalian cells, CRISPR/Cas9 now enables precise genetic modifications in gut bacteria, allowing scientists to harness the microbiome as a therapeutic platform. By leveraging this technology, probiotic strains can be enhanced to produce higher levels of short-chain fatty acids (SCFAs), from dietary fibers and host glycans. The ability to accurately add, delete, or modify genes in these microbes not only improves their survival in the gastrointestinal environment but also amplifies the production of metabolites with demonstrated cardiovascular benefits (Mietus-Snyder *et al*., 2023).

Recent metabolic reconstructions of over 800 gut microbiota species have illuminated key enzymes and pathways responsible for SCFA biosynthesis, providing a blueprint for designing microbes with superior metabolic output (Rahmati *et al*., 2025). By manipulating these pathways, it becomes possible to enhance butyrate and propionate production, thereby improving intestinal homeostasis and metabolic profiles in individuals with metabolic syndrome or diseases associated with gut metabolite imbalances (Wang *et al*., 2022). Such precision engineering transforms the microbiome from a passive participant in metabolism to an active therapeutic agent.

For instance, another approach involves engineered *E. coli* harboring plasmids encoding diverse CRISPR systems, including FnCas12a, SpRY and SpCas9, targeting Bt1754, a conserved gene involved in carbohydrate utilization in Bacteroides species. By excising genomic segments as large as 50 kb, researchers demonstrated the ability to manipulate metabolic gene clusters in *Bacteroides thetaiotaomicron* with remarkable precision. Among the systems tested, CRISPR/FnCas12a showed the highest editing efficiency and demonstrated applicability across multiple Bacteroides strains, including B. fragilis, B. ovatus, B. uniformis and *B. vulgatus*, highlighting its versatility for microbiome engineering (Zheng *et al*., 2022). Furthermore, CRISPR/Cas9 technology could be used to generate hyper-resilient probiotic strains that survive the gastrointestinal tract and release SCFAs more consistently, thus improving vascular health (Mu *et al*., 2022). The SCFA biosynthesis genes may be expressed more to increase the synthesis of butyrate or propionate, which is already known to affect endothelial barrier integrity, vascular tone and lipid metabolism (Fig. 3) (Guo *et al*., 2022; Jan *et al*., 2024).

Table 3: Comparative analysis of SCFA-based strategies and conventional anti-inflammatory therapies in atherosclerosis

Feature	SCFA-based precision strategies	Statins	PCSK9 inhibitors	IL-1β blockers	Colchicine	References
Therapy type	Microbiome-derived metabolites / dietary & engineered approaches	Synthetic drugs	Monoclonal antibodies	Monoclonal antibodies	Natural alkaloid	(Zhang *et al*., 2022)
Primary mechanism	Modulation of gut microbiota, activation of GPCRs (GPR41/43/109A), HDAC inhibition, immune regulation	Inhibition of HMG-CoA reductase → ↓ cholesterol synthesis	Inhibition of PCSK9 → ↑ LDL receptor recycling	Inhibition of IL-1β → ↓ systemic inflammation	Inhibition of microtubule polymerization → ↓ neutrophil activation	(Liu *et al*., 2023; (Hu *et al*., 2022)
Primary target	Gut–heart axis, immune system, endothelial function	Lipid metabolism	Lipid metabolism	Inflammatory cytokines	Inflammatory pathways	(Yukino-Iwashita *et al*., 2022; (Feng *et al*., 2025)
Effect on atherosclerosis	Reduces vascular inflammation, improves endothelial function, modulates lipid metabolism, inhibits plaque progression (preclinical evidence)	Reduces LDL, stabilizes plaques, improves endothelial function	Markedly reduces LDL, plaque stabilization	Reduces vascular inflammation and cardiovascular events	Reduces inflammation and risk of recurrent cardiovascular events	(Chang et al., 2024)

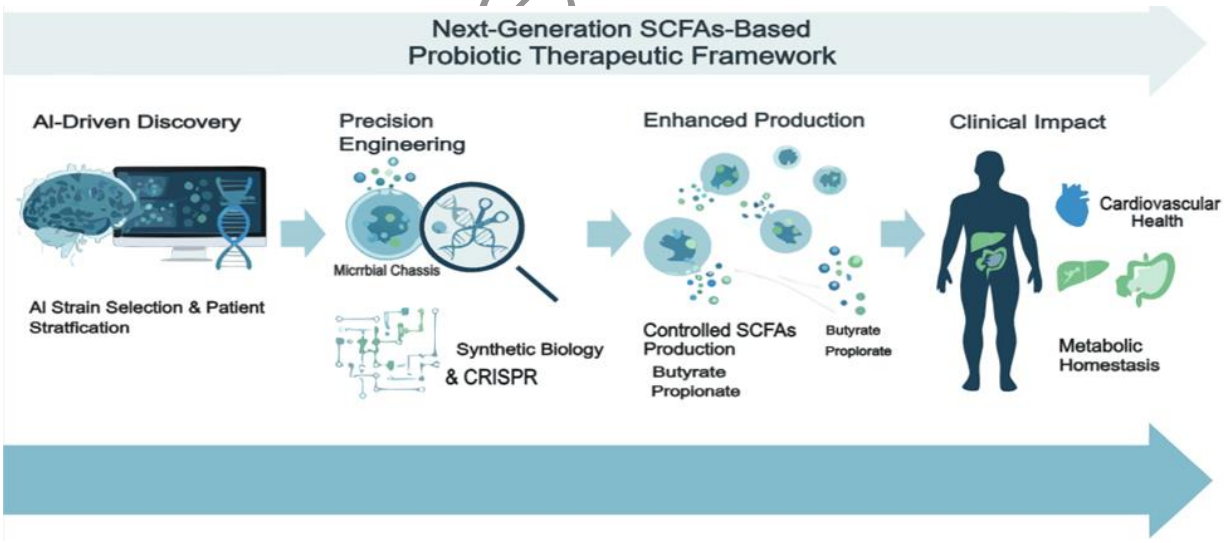

Fig. 2: Schematic overview depicting AI-guided selection and CRISPR/Cas9-enabled engineering of probiotic chassis for controlled SCFA production, linking gut microbiome modulation to improved cardiovascular health and metabolic homeostasis.

AI-driven approaches for patient stratification and microbiome modulation

Machine learning (ML) and artificial intelligence (AI) are transforming the design of SCFA-producing probiotics for cardiovascular diseases, including atherosclerosis, dyslipidemia and endothelial dysfunction (Majumder *et al*., 2025). By integrating multi-omic data—genomics, metabolomics, microbiomics and clinical outcomes—these

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tools accelerate strain discovery, functional decoding, formulation and clinical testing (Fig. 3). Given the gut microbiome's inter-individual variability and functional plasticity, AI-driven stratification can predict responses to dietary or probiotic interventions by modeling microbial resilience, metabolic activity and host-specific factors such as genetics, immune status and prior drug exposure. ML algorithms can also anticipate longitudinal shifts in microbiome composition driven by medications, environments, or lifestyles, enabling personalized optimization. For example, AI-based adaptive regression models like ABIOME can identify probiotic strains or consortia that maximize butyrate or propionate production while minimizing competitive by-products (Asar *et al*., 2025).

Furthermore, ML algorithms can also be used to predict the compatibility of excipients, enabling pharmaceutical scientists to create probiotics that are stable and compatible with the most frequently used cardiovascular drugs, such as statins or PCSK9 inhibitors. Artificial neural network (ANN) models can classify strains with high accuracy using functional genetic markers. Nevertheless, SVM classifiers and k-mer feature selection-based systems, such as iProbiotics, can quickly distinguish between probiotic and non-probiotic microorganisms (Wu *et al*., 2022). In addition to taxonomy, ML incorporates transcriptomic and metabolomic networks, including those of *Lactobacillus reuteri*, to predict the presence of antimicrobial or anti-inflammatory gene clusters of interest in vascular protection. The high-throughput in silico approach to screening lactic acid bacteria isolates has already demonstrated that bioactive strains with potent activity can be selected before in vitro validation, thereby simplifying the pipeline in cardiovascular therapeutics (Saxena *et al*., 2024).

Moreover, Convolutional neural networks (CNNs), trained on large datasets of digital electrocardiograms (EKGs) linked to clinical records, have demonstrated the ability to detect asymptomatic left ventricular dysfunction, silent atrial fibrillation and hypertrophic cardiomyopathy (Schots *et al*., 2025). Notably, these models can also infer demographic characteristics such as age, sex and race from EKG signals. In parallel, deep learning (DL) models integrating EKG data with echocardiographic information—extracted using natural language processing (NLP)—have achieved highly accurate classification of ventricular function. These models can estimate left ventricular ejection fraction with a mean absolute error as low as 5.84% and predict composite outcomes such as right ventricular systolic dysfunction or dilation with strong discriminative performance (area under the curve ≈ 0.84). Collectively, these findings highlight the potential of AI-enhanced EKG analysis as a non-invasive, scalable screening tool for early detection of cardiovascular abnormalities (Chowdhury, *et al*., 2025).

DISCUSSION

Atherosclerosis, which is one of the leading causes of cardiovascular disease, develops through the interaction of complicated interactions between lipid metabolism and immune responses. Plaque inflammation is regulated by cytokine- and chemokine-derived protein fragments (Chan *et al*., 2022). In cardiovascular applications, where dosing is constant and tissue exposure is required, such dynamics make it challenging to develop effective therapies. Researchers are also developing modified-release formulations to overcome such challenges, such as liposomal encapsulation and polymeric prodrugs containing short-chain fatty acids (SCFA) that release in particular parts of the gastrointestinal tract or directly into the systemic circulation. The primary aim is to improve targeting of the vascular endothelium and cardiac tissue and to mitigate gastrointestinal adverse effects. Novel concerns, such as the release kinetics and potential consequences of gastric interactions and gut microbiota, will arise from the proposed changes and need to be addressed, particularly in the proposed pre-clinical stage (El Hage *et al*., 2023).

Furthermore, for live engineered probiotics, developers are required to demonstrate genetic stability, the absence of virulence factors and predictable colonization. For encapsulated SCFAs or prodrugs, chemical characterization, long-term stability tests and release times should be determined (van der Hee & Wells, 2021). The design of clinical trials should align with regulatory requirements, which may differ from conventional cardiovascular drug protocols. Validated surrogate endpoints, strong placebo controls and reproducible manufacturing processes are required to demonstrate efficacy, such as reductions in LDL cholesterol or vascular inflammation. Regulators require evidence that the long-term use of SCFAs will not trigger horizontal gene transfer or lead to a shift in host microflora, which can become dysbiotic (Hoffelner *et al*., 2025).

SCFA has varied effects by inhibiting HDAC, activating G-protein-coupled receptors (GPCRs) and regulating immune and endothelial functions. Any therapeutic activity is unlikely to be captured by analyzing plasma SCFA levels (Verm *et al*., 2024). New methods involving multi-omics biomarkers, such as metabolomics, transcriptomics and microbiome profiling, are potentially more indicative of functional responses in heart tissues. Imaging of tissue uptake and metabolic fate could be further clarified using imaging techniques such as PET or MRI with SCFA-labelled tracers. These would enhance dose-response investigations and facilitate regulatory acceptance by providing a direct connection between SCFA exposure and biological effects. In addition, dosing

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plans must consider formulation, site location, receptor selectivity and any synergies with dietary fiber or co-administrative medications, as well as the molar amount (Hu *et al*., 2022).

AI and machine learning technologies enable the creation of individualized SCFA therapies. Genomic, metabolomic and microbiome data can be integrated into models to identify patient subgroups with the highest likelihood of responding to a particular intervention. For example, patients with microbiomes enriched in propionate-forming gene clusters may benefit from probiotics that produce propionate, combined with lipid-reducing agents (Zhang *et al*., 2023). On the other hand, patients with a low butyrate-producing capacity would need butyrate prodrugs or synbiotics to re-establish SCFA balance. Adaptive algorithms may be employed to adjust the dose in response to continuous biomarker monitoring, thereby achieving SCFA therapeutic targets that reduce side effects, as seen in precision medicine for cardio SCFAs (Dakal *et al*., 2025).

Lastly, the SCFAs should not be viewed as stand-alone treatments but rather as components of a comprehensive treatment ecosystem. The combination of strategies, i.e., interventions based on SCFA and established lipid-lowering medications, anti-inflammatory agents, or lifestyle changes, can potentially have an additive or synergistic effect (Ragavan & Hemalatha, 2024). Such regimens can be designed, interactions predicted and dosing strategies optimized with the assistance of AI-based modeling. In the long term, repeated feedback between predictions from computational models, outcomes of clinical trials and actual outcomes will inform treatment strategies, as has been done with biologics and immunotherapies in other domains (Popeijus *et al*., 2021).

CONCLUSION

Growing evidence positions short-chain fatty acids as pivotal mediators linking the gut microbiome to vascular inflammation and atherogenesis. By modulating immunometabolic pathways, SCFAs can improve endothelial integrity and plaque stability, offering a biologically plausible and mechanistically distinct strategy for attenuating cardiovascular risk beyond conventional lipid-lowering and systemic anti-inflammatory drugs. Advances in engineered probiotics, pro-drug formulations and CRISPR/Cas9-based strain optimization promise to overcome limitations in bioavailability and inter-individual microbiota variability, while AI-driven patient stratification and symbiotic design open the door to precision delivery of SCFA-based interventions. Nonetheless, several research priorities must be addressed to translate these preclinical insights into safe and effective therapies. These include the identification of validated biomarkers reflecting SCFA activity, such as circulating SCFA levels, FFAR2/FFAR3 receptor expression, inflammatory markers (CRP, IL-6, TNF-α) and gut barrier markers (LPS, zonulin). Further priorities are optimizing dosing regimens through rigorous pharmacokinetic studies and designing early-phase clinical trials to evaluate safety, efficacy and mechanistic outcomes in humans. Integrating SCFA biology into therapeutic frameworks may shift atherosclerotic cardiovascular disease management from a one-size-fits-all model toward a personalized, microbiome-targeted paradigm, ultimately improving cardiovascular outcomes through precision modulation of host-microbiome interactions.

Acknowledgments
Not applicable.

Authors' contributions
Ming Liu, Ye Chen, Qingru Meng, Zhenrui Tang contributed equally to the study design, execution, data acquisition, figure preparation, analysis, interpretation and final approval of this article.

Funding
Not applicable. There is no fundings for this study.

Data availability statement
Not applicable (as no new data is produced in this study. It is a review article.).

Ethical approval
Not applicable

Conflict of interest
The authors declare no conflict of interest.

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