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Posted Date: 27 January 2026

doi: 10.20944/preprints202601.2076.v1

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Review

The Immune-Metabolic Axis in Atherosclerosis: Decoding the Influence of Gut Microbiota and Microbiota-Derived Metabolites

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Abstract

Cardiovascular disease (CVD) continues to be the leading non-communicable disease and the main cause of death worldwide, with atherosclerosis being the primary underlying condition factor. Emerging evidence highlights the crucial role of the host microbiota in regulating immune responses and metabolic pathways involved in atherogenesis. Gut and oral microbiota imbalance has been associated with atherosclerosis development, marked by a decrease in anti-inflammatory, butyrate-producing taxa such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Blautia*, along with an increase in pro-inflammatory bacteria like Enterobacteriaceae, *Streptococcus* spp., and *Chlamydia pneumoniae*. The detection of oral microbes within vascular and atherosclerotic lesions further connects oral health with cardiovascular outcomes. Microbial metabolites, such as trimethylamine-N-oxide (TMAO) and microbial-associated molecular patterns, have been shown to increase the risk of coronary heart disease. Conversely, certain gut bacteria, notably *Akkermansia muciniphila*, *Bacteroides dorei*, and *Bacteroides vulgatus*, exhibit protective effects by reducing atherosclerotic lesions and systemic inflammation. Additionally, gut microbiota-derived metabolites, particularly short-chain fatty acids (SCFAs) and bile acid derivatives, regulate immune homeostasis and lipid metabolism via GPR41 and GPR43 receptors. Although microbial signatures associated with atherosclerosis remain debated, growing evidence supports the microbiota and its metabolites as integral to the immune-metabolic axis influencing CVD. Understanding these dual roles may guide the development of microbiome-targeted interventions, including dietary modifications, prebiotics, probiotics, and receptor agonists, to prevent and manage atherosclerosis.

Keywords: Atherosclerosis; Trimethylamine-oxide; short chain fatty acids; gut microbiota; Dysbiosis

1. Introduction

Cardiovascular diseases (CVDs) consist of various conditions that affect the heart and blood vessels, including coronary artery disease, cerebrovascular disease, rheumatic heart disease, and many more. The World Health Organization (WHO) reports approximately 17.9 million deaths worldwide each year due to CVDs. Myocardial infarctions and strokes account for 80% of total CVD deaths, with one-third of deaths in individuals under the age of 70. In the current 21st century, the primary cause of mortality in India is CVDs. CVDs affect the Indian population 10 years earlier than their European counterparts [1]. In Western countries, a quarter of deaths due to CVDs happen before 70 years of age, whereas half of CVD-related deaths occur before 70 years in India [2]. Moreover, countries with lower incomes, like India, have significantly higher death rates due to CVD compared to middle and high-income nations [3]. The mortality rate from CVDs doubled to 2.8 million in 2016, up from 1.3 million deaths in 1990, with a 34.3% increase in the crude death rate. Most CVD deaths

occur in people over 70, but there is a significant number of deaths in younger age groups as well. In 2016, India, which accounts for 17.8% of the world's population, was responsible for 23.1% of the global Disability-Adjusted Life Years (DALYs) caused by ischemic heart disease, 14.0% due to stroke, and a significant 37.6% due to rheumatic heart disease. CVDs represent nearly 30% of all non-communicable diseases (NCDs) in India, with atherosclerosis being the leading cause. The development of atherosclerosis is associated with traditional risk factors, altered lifestyle, and hereditary risk factors. Atherosclerosis often leads to ischemic heart disease (IHD), which is increasingly affecting younger individuals in India with an age of less than or equal to 45 years. In some cases, sudden cardiac death (SCD) can be a symptom of IHD in younger individuals [3]. Atherosclerosis is characterized by a chronic inflammatory process that begins with endothelial injury, leading to lipid accumulation and plaque formation within the intima. The term 'atherosclerosis' is derived from 'atherosis', referring to the accumulation of lipid-laden macrophages, and 'sclerosis', referring to the fibrosis of the arterial wall with smooth muscle cells, leukocytes, and connective tissue [3]. This process involves a complex interaction among dysregulated lipid metabolism, acute inflammation, and vascular cell dysfunction. Additionally, endothelial cells, smooth muscle cells (SMCs), and immune cells, including innate effector cells such as macrophages and adaptive lymphocytes such as T cells and B cells, are involved [4]. In recent years, the involvement of gut microbiota has added another layer of complexity to an already complex system. Microbiota affects host metabolism, immunity, and vascular function through various bioactive metabolites, including trimethylamine-N-oxide (TMAO), bile acid derivatives, short-chain fatty acids (SCFAs), and tryptophan metabolites. Specifically, they can influence immune cell polarization, endothelial function, and oxidative stress pathways [6]. Additionally, microbiota dysbiosis can trigger systemic inflammation by compromising the intestinal permeability and lipopolysaccharide (LPS) translocation, linking gut-derived signals to vascular health injury.

A more comprehensive and detailed mechanistic framework for atherosclerosis can be created by integrating the mechanisms of oxidative stress, immune activation, and microbiota-derived metabolites. This perspective highlights new therapeutic opportunities targeting the microbiota-metabolite-immunity axis and bridges the gap between traditional and emerging risk factors.

2. Conventional and Emerging Cardiovascular Risk Determinants

2.1. Traditional Risk Factor: The Chronic Driver of Vascular Injuries

The growing prevalence of atherosclerotic cardiovascular disease (ASCVD) can be attributed to risk factors such as dyslipidemia, hypertension, smoking, diabetes mellitus, dietary habits, and a sedentary lifestyle. These risk factors can activate common pathogenic mechanisms, such as endothelial dysfunction, oxidative stress, and inflammatory signalling. For example, dyslipidemia is characterized by elevated low-density lipoprotein (LDL) cholesterol, which can lead to the formation of oxidized LDL (oxLDL). These oxLDL particles are potent pro-inflammatory antigens that contribute significantly to vascular damage [5]. Obesity is strongly associated with cardiovascular issues and is a major global health concern. Meanwhile, some studies point to an "obesity paradox" that challenges the idea of obesity as a health risk. More research is necessary to clarify these findings [8]. Hypertension worsens this condition by increasing shear stress on blood vessels, which can result in endothelial injury. Research indicates that high blood pressure can cause significant oxidative stress, further weakening vascular integrity [9]. Moreover, elevated glucose levels from diabetes accelerate the formation of advanced glycation end-products (AGEs), intensifying oxidative stress within blood vessels [6]. Dietary habits significantly influence cardiovascular health. The American Heart Association (AHA) recommends a Mediterranean diet (MD) rich in unprocessed foods, dietary fibre, and healthy fats, with less dairy products, which are linked to lower rates of heart disease [11]. Psychological factors also influence cardiovascular health, where depression increases the risk of CVD, and stress plays a role in the development of atherosclerosis. [7]. Together, these factors form a vicious cycle that aggravates the risk of cardiovascular disease. Evidence from both population

studies and mechanistic research shows that these traditional risk factors closely interact with the body's immune system and gut microbial metabolism, collectively affecting the inflammatory state of blood vessels.

2.2. Emerging and Non-Classical Risk Factor:

The human gastrointestinal (GI) tract contains a diverse and active microbiota, supported by its nutrient-rich environment [8]. The gut microbiota consists of over 10 trillion microbial cells, including various symbiotic microorganisms. These microorganisms play a vital role in modulating immune responses and metabolic processes through their metabolites [14]. Due to their broad metabolic capabilities, they have been described as a "metabolic organ". [9]. Metagenomic sequencing of microbial DNA has revealed the vast diversity of the gut microbiota [10]. Microbiota dysbiosis has emerged as a significant contributor to the pathophysiology of ASCVD [11]. Changes in gut microbial composition can lead to increased production of pro-atherogenic metabolites, TMAO and secondary bile acids. At the same time, it reduces the synthesis of anti-inflammatory SCFAs. This dysbiotic shift maintains a systemic pro-inflammatory environment, increases oxidative stress, and disrupts endothelial homeostasis. For example, a metagenome-wide association study (MWAS) of individuals with ACVD showed differences from healthy subjects, identifying higher levels of taxa from the Enterobacteriaceae family, such as *Escherichia coli*, *Klebsiella* spp., *Enterobacter aerogenes*, and bacteria from the oral cavity, including *Streptococcus* spp., *Lactobacillus salivarius*, *Solobacterium moorei*, and *Atopobium parvulum* in ACVD patients [18]. In contrast, ACVD patients showed lower levels of beneficial bacteria such as *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, which are known butyrate producers, as well as other common gut microbiota members like *Bacteroides* spp., *Prevotella copri*, and *Alistipes shahii* [12]. A study using terminal restriction fragment length polymorphism (T-RFLP) revealed a higher Firmicutes/Bacteroidetes (F/B) ratio in individuals with coronary artery disease (CAD) than in healthy individuals. The Firmicutes phylum mainly comprises *Lactobacillales* and *Clostridium*, and the Bacteroidetes phylum, including *Bacteroides* and *Prevotella* [13]. Research has also underscored the diet-microbiota interaction concerning cardiovascular disease [14]. Metagenomic studies have revealed a higher abundance of *Collinsella*, Enterobacteriaceae, and *Streptococcus* spp. in patients with atherosclerosis, whereas *Roseburia* and *Eubacterium* are more commonly found in healthy individuals [21].

Further investigations have identified *Chryseomonas*, *Veillonella*, and *Streptococcus* in atherosclerotic plaques and changes in cholesterol levels [15]. Furthermore, *Helicobacter pylori*, known for causing gastric ulcers, has been associated with atherosclerosis [16]. A reduction in genera such as *Blautia*, *Collinsella*, and some unclassified Erysipelotrichaceae and Ruminococcaceae has been observed in patients with heart failure compared to healthy controls. Notably, *Blautia* is associated with anti-inflammatory effects [24], and *Akkermansia muciniphila* has been shown to enhance gut barrier integrity and protect against atherosclerosis [17].

Several bacterial species, such as *Chlamydia pneumoniae*, *Staphylococcus* spp., *Streptococcus* spp., *Klebsiella pneumoniae*, *Proteus vulgaris*, *Burkholderia* spp., and *Pseudomonas aeruginosa*, have been associated with the accelerated progression of cardiovascular disease [18]. Virome studies in patients with cardiovascular disease have reported a higher prevalence of bacteriophages, especially those associated with *Propionibacterium*, *Pseudomonas*, and *Rhizobium*. This contradicts the virome of healthy individuals, which is more enriched in eukaryotic viruses such as Lymphocystis virus (LCV) and Torque teno viruses (TTV). The findings suggest that the presence of bacterial and viral DNA elements in the bloodstream could be associated with increased circulating DNA in individuals with cardiovascular disease, a connection that warrants further investigation [19].

Earlier studies and investigations underscored the connection between atherosclerosis development and infections, such as those in the oral cavity, respiratory system (including *Chlamydia pneumoniae*), and those caused by *Helicobacter pylori* [20]. Furthermore, the previous study showed the presence of periodontal bacteria in atherosclerotic plaques [21]. Various other studies further confirmed the presence of bacteria like *P. gingivalis* and *A. actinomycetemcomitans* in these plaques

[22,23]. The origin of microbes and their association with CVDs are listed in Table 1. Recent investigations have continued to link the oral microbiota and atherosclerosis, underscoring the significance of oral bacteria in the pathogenesis of the disease [24].

Table 1. Oral and gut microbiota associated with CVDs.

SL no.	Diseases	Origin of microbiota	Types of microbiota present	Inference	Reference
1.	Coronary heart disease	Oral	<i>Porphyromonas gingivalis</i> and <i>Aggregatibacter actinomycetemcomitans</i>	Provide evidence for the presence of viable oral pathogens at the vascular sites and also at the atherosclerotic plaque.	[22]
2.	Coronary Artery Disease	Gut	Phylum Bacteroidetes, Firmicutes	Decrease abundance of phylum Bacteroidetes and increase in phylum Firmicutes in patients with CAD	[13]
3.	Atherosclerotic cardiovascular disease (ACVD)	Oral and Gut	Phylum Proteobacteria, Actinobacteria, Firmicutes, Cyanobacteria and Bacteroidetes.	Proteobacteria (48.3%) and Actinobacteria (40.2%), and three less dominating phyla: Firmicutes (4.0%), Cyanobacteria (3.9%) and Bacteroidetes (2.2%) in both symptomatic and asymptomatic patients	[253]
4.	Atherosclerotic cardiovascular disease (ACVD)	Oral cavity	<i>Veillonella</i> and <i>Streptococcus</i>	Bacteria from oral cavity may correlate with the disease marker of atherosclerosis.	[15]
5.	Atherosclerotic cardiovascular	Gut	<i>Enterobacteriaceae</i> and <i>Streptococcus</i> spp.	Increase abundance of Enterobacteriaceae and	[12]

	disease (ACVD)			<i>Streptococcus</i> spp. in ACVD patients compared to normal.	
6.	Atherosclerotic cardiovascular disease (ACVD)	Gut	<i>Roseburia intestinalis</i>	Provide protection against atherosclerosis	[14]
7.	Atherosclerotic cardiovascular disease (ACVD)	Gut	<i>Akkermansia muciniphila</i>	Provide protection against atherosclerosis	[17]
8.	Cardiovascular disease	Gut	<i>Chlamydia pneumoniae</i> , <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Klebsiella pneumoniae</i> , <i>Proteus vulgaris</i> , <i>Burkholderia</i> and <i>Pseudomonas aeruginosa</i>	Associated with CVD progression	[18]
9.	Atherosclerotic cardiovascular disease (ACVD)	Oral and gut	<i>Chlamydia pneumoniae</i> and <i>Helicobacter pylori</i>	Associate with progression of atherosclerosis	[20]
11.	Atherosclerotic cardiovascular disease (ACVD)	Oral	<i>Anaeroglobus</i>	Most abundant oral bacteria present in the symptomatic ACVD patient	[254]
12	Atherosclerotic cardiovascular	Oral	<i>Chryseomonas</i>	May contribute to the progression of Atherosclerosis	[255]

	disease (ACVD)				
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3. Lipid Peroxidation in Vascular Inflammation

Lipid peroxidation is a crucial internal chain reaction that significantly contributes to lipid oxidation. When lipids with carbon-carbon double bonds are attacked by free radicals or non-radical species, they lose a hydrogen atom from a carbon and gain an oxygen atom. This process results in the formation of lipid peroxy radicals and hydroperoxides [25].

Lipids play a significant role in the onset of cardiovascular diseases, mainly due to their predisposition to oxidation. These lipids, present in the bloodstream and various tissues, may bind with lipoproteins or albumin. Lipoproteins have a core filled with cholesterol esters and triglycerides, surrounded by free cholesterol, phospholipids, and apolipoproteins, which are the main transporters of lipids that do not dissolve in water. Lipoproteins are categorized into various types based on their size, lipid makeup, and apolipoproteins, including chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein (a) (Lp(a)). These lipoproteins play a crucial role in processing and transporting dietary lipids from the intestines and lipids from the liver. HDL plays a crucial role in reverse cholesterol transport (RCT), facilitating the transport of cholesterol from the body's tissues back to the liver and intestines. On the other hand, LDL mainly transports cholesterol to cells, which raises the risk of heart disease. Oxidative mechanisms in the development of atherosclerosis are complex and influenced by multiple factors. Initially, LDL particles in the arterial wall can undergo varying degrees of oxidation, which contributes to the progression of atherosclerosis. OxLDL can lead to endothelial damage, promote the adhesion of inflammatory cells, and induce macrophage transformation [26]. This process contributes to endothelial dysfunction by suppressing endothelial nitric oxide synthase (eNOS), stimulating inflammatory cytokine release, and promoting platelet aggregation. Oxidized LDL induces the activation of pro-inflammatory genes, including (tumor necrosis factor α) TNF α , (interleukin 1 β) IL-1 β , and (interleukin 6) IL-6, through the stimulation of peroxisome proliferator-activated receptor gamma (PPAR γ) [27]. Furthermore, lipid peroxidation byproducts elevated the expression of monocyte chemoattractant protein-1 (MCP-1), interferon- γ -inducible protein-10, and cyclooxygenase-2 (COX-2) and facilitated the transcriptional activation of nuclear factor (NF)- κ B following the uptake of modified LDL. These substances further exacerbate atherosclerosis by producing leukotrienes, acrolein, and other inflammatory agents that activate endothelial and foam cells and cause mast cell degranulation, intensifying inflammatory damage [28,29]. The endothelium plays a vital role in regulating vascular tone, maintaining homeostasis, facilitating molecular exchange between the blood and tissues, and signaling immune responses and inflammation [30].

Endothelial dysfunction and damage cause LDL cholesterol to seep into the vessel wall, especially the intima, where it undergoes oxidation. The buildup of cholesterol oxidation products, such as oxysterols and aldehydes, is prominent in atherosclerotic lesions. Scavenger receptors on endothelial cells, like the lectin-like oxidized LDL receptor 1 (LOX-1), facilitate the uptake of oxLDL and contribute to foam cell formation, thus speeding up atherosclerosis. LOX-1 is implicated in endothelial cell apoptosis and is associated with elevated levels of MCP-1 and transforming growth factor β 1 (TGF- β 1). Furthermore, LOX-1 downregulates the activity of eNOS and stimulates the synthesis of matrix metalloproteinases in vascular smooth muscle cells (VSMCs) [31].

Although HDL is considered protective due to its role in reverse cholesterol transport, there is evidence that HDL can be oxidized, altering its beneficial properties into harmful ones [32]. HDLs represent a diverse and functionally complex family of lipoproteins, characterized by multiple subclasses that vary in their physical dimensions, structural morphology, and lipid and apolipoprotein composition. This inherent heterogeneity renders HDLs vulnerable to various

oxidative modifications induced by reactive oxygen species, including peroxy and hydroxyl radicals, aldehyde compounds, and oxidants generated by myeloperoxidase (MPO) [33]. Such changes lead to dysfunctional HDL, as evidenced by reduced sphingosine-1-phosphate levels in patients with coronary artery disease [34]. The oxidation of lipids, driven by free radicals, generates biologically relevant aldehydes, including advanced lipoxidation end products (ALEs), malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and acrolein [35,36]. These oxidation byproducts trigger inflammation, extracellular matrix deposition, and arterial wall remodeling, all of which are vital to the progression of atherosclerosis [37]. Endothelial cells are highly susceptible to 4-HNE-induced damage. A rise in 4-HNE levels decreases NO availability by lowering dimethylarginine dimethylaminohydrolase (DDAH) activity, which can elevate methylarginine levels, diminish eNOS-derived NO production, and consequently, endothelial dysfunction [38]. ALEs also cause monocyte activation and vascular complications by activating inflammatory pathways [39].

In addition, 4-HNE prompts macrophages to produce matrix metalloproteinase-9 (MMP-9) [40] and MMP-2 in vascular smooth muscle cells [41]. These enzymes are responsible for the degradation of collagen fibers and may destabilize atherosclerotic plaques and promote thrombus formation. 4-HNE activates matrix metalloproteinases-1 and -2 in vascular smooth muscle cells. These enzymes not only degrade the extracellular matrix [42], but it also activates protein kinase B (Akt) [41], p38 mitogen-activated protein kinase (MAPK)[43]. Its phosphorylation of c-jun N-terminal kinase (JNK) is also noteworthy [44].

Recent research has highlighted the buildup of 4-HNE-adducts, especially in the smooth muscle cells of the human aorta. This buildup tends to increase with age and is common in people with advanced atherosclerosis [45]. Additionally, 4-HNE levels are elevated in the adventitia, which is associated with the vasa vasorum and microcapillaries found in atherosclerotic lesions [46]. While 4-HNE does not directly affect aortic elastin, it plays a role in its breakdown and decreases its ability to regenerate [47]. Moreover, other oxidant sources within the vessel wall, such as myeloperoxidase, lipoxygenases, mitochondria, and uncoupled eNOS, are often found in human atherosclerotic lesions [48].

4. Immune Cells and Immune Response in Atherosclerosis

Atherosclerosis begins with the retention of apolipoprotein-B-containing lipoproteins, such as LDL, and their oxidative or enzymatic modification within the arterial intima. These modified lipoproteins act as damage-associated molecular patterns that trigger local innate and adaptive immune responses. This chronic condition typically starts with dysfunctional endothelial cells, which are characterized by the upregulation of surface cell adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), intracellular cell adhesion molecule 1 (ICAM-1), and E-selectin [49]. This leads to the recruitment of circulating monocytes and other leukocytes to these regions [50]. The monocytes migrate to the site and transform into macrophages that internalize lipoproteins via scavenger receptors such as SR-A, (cluster of differentiation 36) CD36, and LOX-1, and via pinocytosis. These lipid-laden macrophages transformed themselves into foam cells that secrete proinflammatory cytokines and matrix remodelling enzymes [51]. A significant fraction of CD4⁺ T cells belonging to the T helper type 1 (Th1) group infiltrate the arterial damage in response to LDL. These Th1 cells produce proinflammatory cytokines, including interferon- γ (IFN- γ) and TNF- α [52]. IL-6 produced by arterial walls during atherosclerosis can prompt the liver to initiate an acute-phase response. Activation of the acute-phase response in the liver causes the release of acute-phase reactants, such as (C-reactive protein) CRP, into the bloodstream [53]. The association between elevated CRP levels and myocardial infarction highlights the role of inflammation in myocardial ischemia [54]. CRP concentrations have been identified as an independent marker for forecasting cardiovascular incidents [55]. Although CRP does not directly cause atherosclerosis [55], its role as an indicator of vascular inflammation makes it a valuable marker for assessing statin treatment in patients with intermediate risk levels [56]. The invading monocytes differentiate into macrophages under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and

macrophage colony-stimulating factor (M-CSF), which are secreted by endothelial cells, among others. Macrophages derived from monocytes constitute a significant portion of the cell population in atherosclerotic plaques due to ongoing recruitment, differentiation, and proliferation at the site [57].

Research involving in vitro and in vivo models has shown that macrophages can transform into either an inflammatory M1 type or a less inflammatory M2 type, guided by the type of activation signals they receive [58]. IL-4 or IL-13 can stimulate the development of M2, whereas IFN- γ and lipopolysaccharide trigger classical activation of M1 macrophages. It has been observed that M1 macrophages are laden with lipids, in contrast to M2 macrophages, which hold fewer lipids and are located away from the central lipid area [59]. Identifying these macrophage subsets in live organisms presents difficulties, as over a third of macrophages extracted from the aortas of atherosclerotic mice do not conform to the standard M1 or M2 categories. A study by Kadi *et al.* [60] transformed macrophage into a subset after treatment with oxidised phospholipid. This particular macrophage is characterized by a novel phenotype, referred to as Mox macrophages. This phenotype exhibits a significant upregulation of Nuclear factor erythroid 2-related factor 2 (NRF2) mediated gene expression involved in redox reactions. Their findings showed that Mox macrophages accounted for approximately 30% of the total macrophage population in the advanced atherosclerotic lesions in *Ldl*^{-/-} mice.

Macrophages are known for their adaptability and interactions with other cell types, notably T cells, which can influence their polarization in their immediate surroundings. Interestingly, vascular smooth muscle cells can transform into macrophage-like cells in response to lipid accumulation under controlled conditions [61]. In vivo experiments tracking cell fate in murine model have revealed that roughly 30% of smooth muscle cells within atherosclerotic lesions display attributes typically associated with macrophages. This observation is consistent with findings in human lesions [62–64]. A significant portion of these transformed smooth muscle cells show similarities to the Mox cell type in the plaques of *ApoE*^{-/-} mice [62].

4.1. Innate Immunity in Atherosclerosis

In atherosclerosis, oxLDL plays a significant role in triggering macrophage activation (Figure 1), where the NF- κ B moves into the nucleus [65]. Within atherosclerotic lesions, these macrophages are known to express multiple Toll-like receptors (TLRs). These receptors can detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). TLR2 and TLR4 are activated by modified LDL and its by-products [66]. Furthermore, elements such as heat shock proteins, bacterial toxins, and viral glycoproteins present in the lesions also serve as both internal and external triggers for TLRs [52]. The interaction of these TLRs, via the (Myeloid Differentiation Primary Response Gene88) MyD88 adaptor protein, leads to the activation of signalling pathways that result in the secretion of pro-atherosclerotic cytokines such as IL-1 β and IL-18 [67]. Moreover, the innate immune system is further activated by products of LDL oxidation, such as lysophosphatidylcholine and oxidized non-esterified fatty acids, which are generated by the enzyme lipoprotein-associated phospholipase A2 (Lp-PLA2) [68].

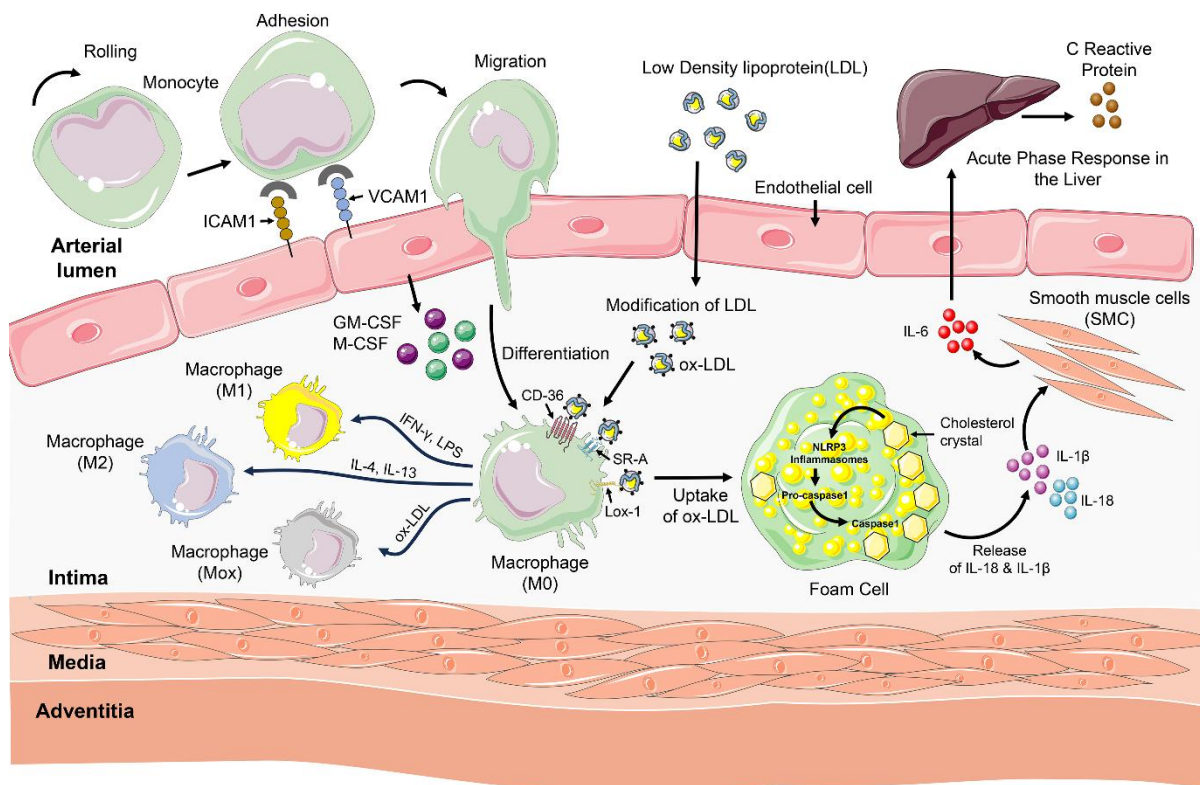


Figure 1. Innate immune response in atherosclerosis. The schematic illustrates the monocyte recruitment, differentiation, and foam cell formation during atherogenesis. Circulating monocytes adhere to activated endothelium via ICAM1 and VCAM1, migrate into the intima, and differentiate into macrophages that uptake oxidized LDL, forming foam cells and releasing proinflammatory cytokines contributing to plaque progression. The Figure illustration was prepared using Servier Medical Art, licensed under a creative commons' attribution 4.0 international license

Cholesterol crystals in foam cells are known to activate the (NOD-like receptor 3) NLRP3 inflammasome, which converts pro-caspase-1 into its active form, caspase-1. This activation results in the production and release of IL-18 and IL-1 β , leading to inflammation and immune responses [69]. Inhibiting IL-1 β as a strategy to prevent cardiovascular incidents has been explored in clinical trials [70]. The release of IL-1 β from foam cells also prompts SMCs to produce IL-6, which, in turn, stimulates the liver to initiate an acute-phase response, including the production of CRP [71].

Other innate immune cells, such as neutrophils, mast cells, natural killer (NK) cells, and natural killer T (NKT) cells, are also present in plaques but in smaller numbers than macrophages. In hypercholesterolemic mice, neutrophils are recruited during the early stages of atherosclerosis but are absent in later stages [72]. NK and NKT cells can exacerbate atherosclerosis, likely through the release of IFN- γ [73,74]. However, NKT cells might also limit disease progression by producing the anti-inflammatory cytokine IL-10 [75]. $\gamma\delta$ T cells appear to have no significant effect on atherosclerosis [76]. Although several small populations of innate immune cells are involved at different stages of the disease, macrophages are the main effector cells in the plaque.

4.2. Adaptive Immunity in Atherosclerosis

The adaptive immune system is essential in coordinating the immune response to atherosclerosis. T cells, B cells, and their effector molecules are key players in this condition (Figure 2). Atherosclerosis may not be classified as an autoimmune disease, but compelling evidence from both clinical and preclinical studies showed that autoimmune responses can be observed in individuals with atherosclerosis and in animal models. Two key subsets of T cells, CD4 $^+$ and CD8 $^+$, play a significant role in this process and highlight the adaptive immune system's multifaceted

nature. Antigen-presenting cells (APCs), particularly macrophages within the atherosclerotic plaque, adventitial B cells, and dendritic cells (DCs), are central to modulating adaptive immunity [77]. These APCs migrate to the lymph nodes, where they present the plaque-derived peptides on their MHC (major histocompatibility complex) class I or MHC class II molecules to the naïve CD4⁺ or CD8⁺ T cells, respectively [78]. The interaction between co-stimulatory molecules such as CD28 and CD40L on APCs with T cell receptor (TCR) is essential for inducing clonal proliferation [79] and differentiation of T cells into various effector subsets such as T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), CD4⁺ regulatory T cells (Treg), and CD8⁺ cytotoxic T cells [80]. These specialized effector cells, with immunological memory, migrate from draining lymph nodes to the systemic circulation, where they accumulate in the atherosclerotic plaque [81]. Effector cells expressed receptors such as CCR5 [82], CXCR6 [83], and CXCR3 [84] as homing receptors for the atherosclerotic lesion. For instance, Th1 cells, which are predominant dominant in atherosclerotic lesions, are characterized by the expression of T-box transcription factor (T-bet)[85]. These cells secrete pro-inflammatory cytokines like IFN- γ and TNF, which polarize macrophages towards M1 effector cells and T cells, amplifying the atherogenic inflammation [86]. IFN- γ has a dual role; while it restricts the VSMCs' proliferation [91], it also accelerates the degradation of collagen [92], leading to plaque instability. On the other hand, TNF- α increased the lesion size by promoting leukocyte infiltration [87] and elevating the LDL levels [88]. Meanwhile, Th2 T helper cells, which express transcription factor GATA-binding protein 3 (GATA3), are essential for establishing humoral immunity [89]. In addition, Th17 cells, expressing the transcription factor RARA-related orphan receptor gamma (ROR γ), represent a significant subset of CD4⁺ T cells in atherosclerosis [90]. The actions of Th2 and Th17 cells can swing either toward pro- or anti-atherogenic effects depending on the cytokines they release [91]. For instance, IL-4 from Th2 cells promotes atherogenic [92], while IL-5 and IL-13 can inhibit the Th1 response, presenting a protective mechanism against atherosclerosis [93]. In addition, IL-5 promotes the production of antibodies against the oxLDL by inducing B1 cell maturation. Similarly, cytokines such as IL-17, IFN- γ , IL-6, and GM-CSF produced by Th17 not only accelerate atherosclerosis progression but also worsen leukocyte accumulation in plaques [94,95]. Treg cells play a vital role in maintaining immune balance by secreting essential anti-inflammatory cytokines such as IL-10 and TNF- β . They are instrumental in preventing atherosclerosis by inhibiting the proliferation and functional activity of CD4⁺, CD8⁺, B cells, NKT cells, and APCs, as well as cytokine production. Furthermore, Treg cells enhance macrophage efferocytosis, a process critical for cellular cleanup and tissue health [96]. However, in the presence of ApoB100, these beneficial Treg cells can lose CD25 and FoxP3 expression and exhibit a pro-inflammatory Th1/Th17 phenotype with cytotoxic properties [97]. A fraction of Treg cells can convert into T follicle helper cells, thus losing their ability to suppress immune responses and prevent atherosclerosis [98]. MHC class I molecules play a crucial role in presenting apolipoprotein B-derived epitopes to CD8⁺ T cells, which subsequently differentiate into CD8⁺ cytotoxic T lymphocytes (CTLs) [97]. CD8⁺ T cells can either contribute to the progression of atherosclerosis or protect against it. For example, CD8⁺ cytotoxic T cells can promote necrotic core formation by releasing cytotoxic granules, especially perforin-1 and granzymes, to induce apoptosis in macrophages, VSMCs, and endothelial cells. Moreover, they aggravate inflammation and monocytosis in the bone marrow by producing pro-inflammatory cytokines like TNF- α and IFN- γ [99]. Additionally, a specific subset of CD8⁺ T cells with regulatory functions can actively reduce atherosclerosis by limiting the accumulation of macrophages and Th1 cells [108], as well as decreasing B cell-mediated atherogenic antibody production [109].

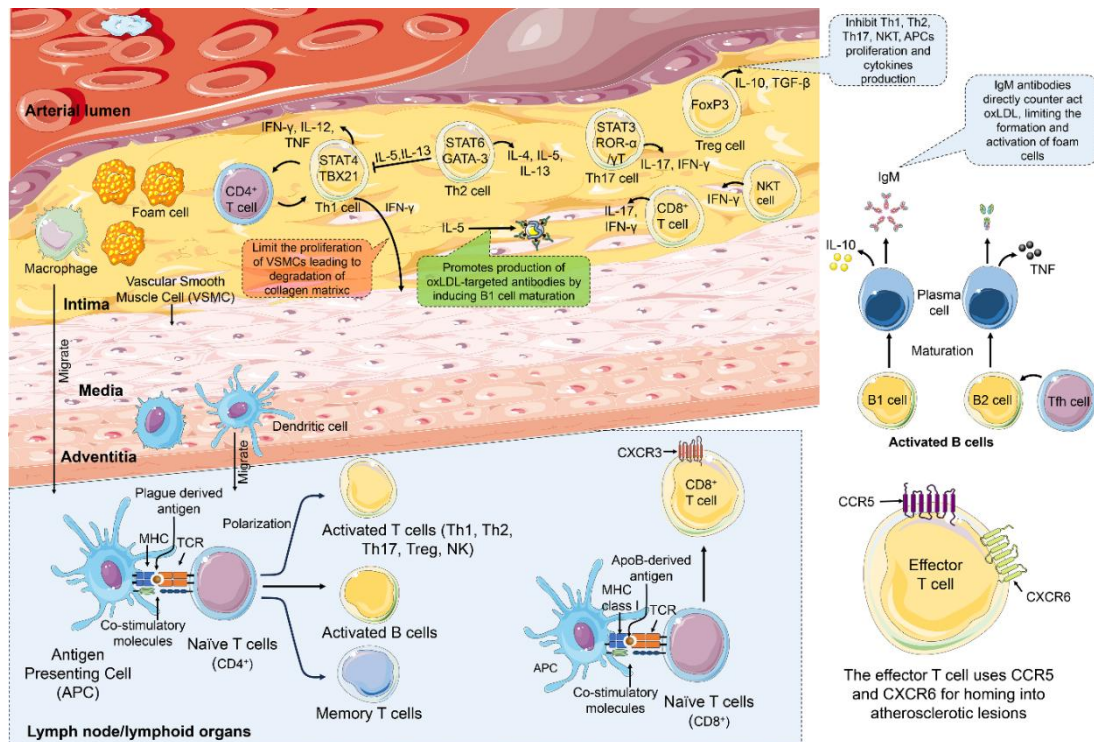


Figure 2. Adaptive immune responses in atherosclerosis. Antigen-presenting cells activate naïve CD4⁺ and CD8⁺ T cells, leading to the differentiation of Th1, Th2, Th17, Treg, and cytotoxic subsets that modulate vascular inflammation. Th1 and Th17 cells promote plaque instability via cytokine secretion, whereas Treg cells exert anti-inflammatory effects through IL-10 and TGF- β . Activated B1 cells generate protective IgM antibodies targeting oxidized LDL, while B2 cells and Tfh cells contribute to pro-atherogenic immune activation. Effector T cells expressing CCR5 and CXCR6 migrate to atherosclerotic lesions, sustaining chronic inflammation and plaque progression. The Figure illustration was prepared using Servier Medical Art, licensed under a Creative Commons' Attribution 4.0 International license.

B cells, like T cells, detect antigens and other foreign molecules with the B cell receptors (BCRs). These receptors play a significant role in the activation, maturation, and differentiation of B cells into antibody-producing plasma cells. B cells are broadly categorized into two types, B1 cells and B2 cells [100]. B1 cells have a unique ability to mature independently into B1 plasma cells, which secrete IgM antibodies that specifically target oxidized low-density lipoprotein (oxLDL), while also producing the anti-inflammatory cytokine IL-10. This dual action is crucial, as IgM antibodies directly counteract oxLDL, thereby reducing foam cell formation and inhibiting their activation, while IL-10 effectively modulates the immune response and promotes homeostasis [101]. On the other hand, B2 cells rely on T follicular helper (Tfh) cells for their activation and subsequent maturation into B2 plasma cells [102]. These B2 plasma cells release IgG antibodies and pro-inflammatory cytokines like TNF- α , which can, unfortunately, drive the progression of atherosclerosis [103].

5. Gut-Derived Metabolites and Atherosclerosis

The gut microbiome breaks down both diet-derived and host-produced substances, producing metabolites that significantly influence microbial communities and host cells. It is believed that more than half of the metabolites in feces and urine originate from or are altered by the gut microbiota [104]. These metabolites fall into three main categories (1) metabolites that come from daily diet and modified by the gut microbiota, like compound K [105]; (2) metabolites originated from the host and transformed by the gut microbiota, for instance, secondary bile acids [106]; and (3) metabolites that are produced by the gut microbiota, including short-chain fatty acids [107].

These metabolites do not localize in the gastrointestinal tract but instead travel throughout the body, mainly through the small intestine [108]. Depending on the type of cell they interact with, these

metabolites have varying effects on the host cells. For instance, it affects vital functions such as intestinal epithelial regeneration, maintenance of the intestine, and the balance of the mucosal immune system [109].

5.1. Trimethylamine N-Oxide and Its Role in Cardiovascular Disease

Trimethylamine (TMA) is a compound produced in the gut microbiome from dietary components such as betaine, L-carnitine, γ -butyrobetaine (GBB), choline, and various choline-rich compounds [110]. The transformation of choline into TMA is catalyzed by enzymes encoded by the *cutC/D* gene cluster, where CutC represents a glyceryl radical enzyme with choline trimethylamine-lyase activity and CutD signifies a glyceryl radical-activating protein. These enzymes, together with proteins responsible for the construction of microcompartments that isolate acetaldehyde, a TMA by-product, are present across several bacterial phyla, including Firmicutes (e.g., *Clostridium* XIVa strains) [111], Actinobacteria, Proteobacteria (e.g., *Desulfovibrio desulfuricans*, *Desulfovibrio alaskensis*) [112], and *Eubacterium* sp. strain AB3007 [111]. Nonetheless, the Bacteroidetes phylum lacks these Cut genes and the TMA-lyase functionality [110].

The gene duo *cnt A/B* is crucial for synthesizing a two-component oxidoreductase enzyme that converts L-carnitine into TMA, initially producing γ -butyrobetaine in the ileum, which is later converted to TMA in the cecum and colon [113]. Similarly, the genes *yeaW/X* encode an oxygenase and an oxidoreductase, which play a role in the generation of TMA from substrates such as γ -butyrobetaine, L-carnitine, choline, and betaine [114]. A variety of gut microbiota, including Gammaproteobacteria (e.g., *Klebsiella pneumoniae*, *E. coli*, *Citrobacter*, *Providencia*, and *Shigella*), Betaproteobacteria (e.g., *Achromobacter*), Firmicutes (e.g., *Sporosarcina*), and Actinobacteria, possess orthologs and homologs of the *CntA/CntB* and *YeaW/YeaX* genes. However, it is noteworthy that bacteria from the Bacteroidetes phylum do not contribute to TMA production [115]. Romano *et al.*'s research identified eight species within the primary phyla of Firmicutes and Proteobacteria that can metabolize choline to TMA, including *Anaerococcus hydrogenalis*, *Clostridium asparagiforme*, *Clostridium hathewayi*, *Clostridium sporogenes*, *Escherichia fergusonii*, *Proteus penneri*, *Providencia rettgeri*, and strains of *Edwardsiella tarda*, indicating a potential acquisition through horizontal gene transfer [110].

Dietary choices, especially fish and seafood, are high in TMAO and TMA. About 50% of the TMAO consumed is directly absorbed and excreted in urine, while the remaining portion is converted into TMA by TMAO reductase in the gut [116]. Certain gut microorganisms can change TMA into TMAO using TMA monooxygenase [117]. Additionally, TMA and TMAO serve as substrates for gut bacteria to produce dimethylamine (DMA) and formaldehyde, mediated by trimethylamine dehydrogenase (TMADH) and TMAO demethylase [117]. Most TMA formed or ingested in the gut is quickly absorbed into the portal circulation. It is oxidized to TMAO by liver flavin-containing monooxygenases (FMOs), with FMO3 being especially important due to its much higher specificity compared to FMO1 [114].

Plasma TMAO concentrations vary significantly among individuals based on age, diet, and other factors. TMAO levels tend to increase with age, and cholic acid, a bile salt, can boost plasma TMAO levels by promoting FMO3 expression through the bile acid-activated nuclear receptor FXR. TMAO levels are also affected by sex hormones, with testosterone decreasing FMO3 expression and estrogen increasing it. Trimethylaminuria may occur due to the notable decrease in TMAO levels that happens during menstruation [118].

Dietary choices significantly impact TMAO synthesis, with vegetarians usually producing less TMA than omnivores. Diets high in fat or typical Western diets correlate with higher plasma TMAO concentrations. Consumption of foods rich in non-digestible carbohydrates could reduce the production of TMAO by changing the composition of gut bacteria, even though there is evidence of a short-term rise in TMAO levels in the blood after a boost in the consumption of non-digestible starch [118].

TMAO is implicated in the development of CVD, especially atherosclerosis (Figure 3). TMAO levels could be indicative of the likelihood of CVD occurrences and major adverse cardiovascular

events (MACE), such as myocardial infarction, stroke, and death [119]. Research on mice fed with Western diet found a connection between elevated TMAO levels in the blood and several adverse cardiac outcomes. These included cardiac dysfunction, heart fibrosis, increased levels of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), alongside a decrease in anti-inflammatory cytokines like IL-10 [120].

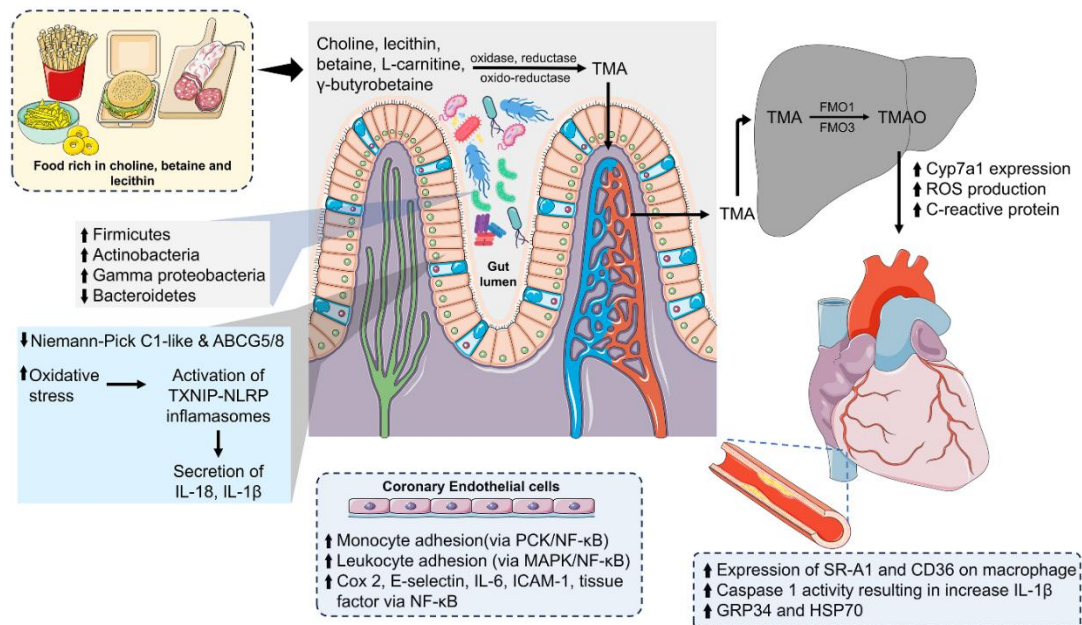


Figure 3. Schematic diagram describing the formation of TMA and TMAO from the dietary intake and its role in various organs. Diets rich in choline, betaine, and lecithin are oxidized and reduced to TMA. TMA is converted into TMAO in the liver using the FMO1/3 enzymes. In the liver, TMAO decreases the expression of *CYP7A1* and increases the production of reactive oxygen species and also CRPs. In the endothelial lining of the heart, it induces monocyte and leukocyte adhesion and also increases the production of Cox2, E-selectin, IL-6, ICAM-1, and tissue factor via NF- κ B. In atherosclerotic lesions, TMAO induces the expression of SR-A1 and CD36 on the macrophage, increases caspase1 activity, and the expression of GPR34 and HSP70. In the gut lumen, TMA increases the abundance of Firmicutes, Actinobacteria, Gamma Proteobacteria but reduces the abundance of Bacteroidetes. In addition, it acts on the colonocyte and reduces the expression of Niemann-PickC1-like-1 and ABCG5/8. TMA increases oxidative stress, thereby releasing IL-18, IL-1 β cytokines. The Figure illustration was prepared using Servier Medical Art, licensed under a Creative Commons' Attribution 4.0 International license. Bacterial icons were taken from the FLATICONS by FREEPIK (<https://www.flaticon.com/>).

TMAO interferes with normal endothelial cell function and contributes to CVD. Application of TMAO to human monocytic THP-1 cells and human umbilical vein endothelial cells (HUVECs) enhances monocyte adhesion via the PKC/NF- κ B pathway, resulting in elevated VCAM-1 levels [121]. In a similar mechanism, exposure of human aortic endothelial cells (HAECs) and vascular smooth muscle cells to TMAO results in greater leukocyte adhesion by activating the MAPK/NF- κ B pathway [122]. TMAO further triggers the release of pro-inflammatory proteins such as cyclooxygenase 2, E-selectin, IL-6, and intracellular adhesion molecule 1 by stimulating NF- κ B [122]. Moreover, TMAO boosts the expression and functionality of tissue factor (TF) in primary human coronary artery endothelial cells (HCAECs) via the NF- κ B pathway, which may lead to atherothrombosis [123].

The cytokines IL-23 and IL-22 can influence atherosclerosis by affecting the composition of pro-atherogenic microbiota and their byproducts, such as TMAO. Inhibiting the IL-23 and IL-22 pathway results in elevated systemic concentrations of TMAO, demonstrating their importance in regulating the microbial generation of TMAO [124]. IL-22 is notably produced by Th17 cells, with IL-23 being

essential for the function of these cells [125,126]. The specific roles of IL-22 and IL-23 in atherosclerosis remain to be fully elucidated.

Individuals suffering from metabolic disorders such as type 2 diabetes and chronic kidney disease exhibit a higher concentration of microbes that produce TMA. In these patients, increased levels of TMAO are associated with signs of inflammation and endothelial dysfunction [127]. TMAO affects cholesterol and sterol metabolism across biological systems, including the bile acid pool, thereby affecting lipid balance [113]. TMAO decreases the activity of the CYP7A1 enzyme, which is essential for bile acid production and cholesterol breakdown. Certain human CYP7A1 gene variations have been linked to lower CYP7A1 activity and an increased risk of atherosclerosis [128].

Intake of TMAO precursors such as choline and carnitine, or direct supplementation with TMAO, can inhibit reverse cholesterol transport. This reduction in activity can be attributed to the lowered levels of specific intestinal cholesterol transporters. Notably, ABCG5/8 promotes cholesterol efflux, and the Niemann-Pick C1-like 1 (NPC1L1) protein aids in the absorption of cholesterol into enterocytes [129]. Additionally, TMAO increases macrophage expression of scavenger receptors CD36 and SR-A1, which cause lipid accumulation and foam cell formation in atherosclerotic lesions [130,131]. OxLDL activates these receptors, and the MAPK/JNK signalling pathway might play a key role in TMAO-induced atherosclerosis [132].

Elevated levels of TMAO trigger NLRP3 inflammasome activation, increasing caspase-1 activity and IL-1 β secretion. Additionally, this process increases the endothelial cells' permeability, aiding in the onset of endothelial damage and the development of atherosclerosis. This phenomenon has been observed in carotid artery endothelial cells (CAECs) and in mice that have undergone partial ligation of the carotid arteries [133]. Furthermore, TMAO is capable of inducing oxidative stress and triggering the activation of the TXNIP-NLRP3 inflammasome, which leads to the release of the inflammatory cytokines IL-18 and IL-1 β in a manner dependent on both concentration and time [134]. In addition, Yue *et al.* found that TMAO activates the NLRP3 inflammasome and stimulates the production of reactive oxygen species (ROS) in fetal human colon cells (FHCs) [135].

In individuals suffering from ischemic stroke, there is a significant correlation between the levels of TMAO and the proportion of pro-inflammatory intermediate monocytes, specifically CD14⁺CD16⁺ [136]. Levels of TMAO are associated with markers of monocyte activation and inflammation, such as sCD14 and sCD163, in individuals with HIV who also have carotid atherosclerosis [137]. Moreover, sCD14 levels have been shown to independently correlate with TMAO levels in untreated HIV-infected patients [138]. Additionally, mice on a choline-rich diet, which increases TMAO synthesis, show higher levels of pro-inflammatory Ly6C high monocytes than those on a standard diet [136].

A study of 271 German adults found a significant association between high plasma TMAO levels and low-grade inflammation. Higher TMAO levels were associated with elevated TNF- α and soluble TNF receptors (sTNF-R p75 and sTNF-R p55). However, no changes were noted in plasma IL-6 and C-reactive protein levels [139]. On the other hand, Chou *et al.* reported a positive correlation between TMAO levels and both IL-1 β and high-sensitivity CRP (hsCRP) in patients with stable angina [140]. CRP is recognized as an inflammation marker used to assess the risk of atherosclerosis and cardiovascular events [139,141]. In vitro studies with endothelial progenitor cells (EPCs) have demonstrated that TMAO induces cellular inflammation and oxidative stress [140].

5.2. Short-Chain Fatty Acids and Their Role in Metabolism

Short-chain fatty acids, which contain 1-6 carbon atoms, are produced through the anaerobic fermentation of non-absorbed nutrients, including resistant starch, dietary fiber, and complex carbohydrates [142]. Acetate, propionate, and butyrate are important SCFAs that are abundant in the cecum and have concentrations of about 130 mmol/kg, which is comparable to what is found in the portal vein [143]. The composition of the gut microbiota, gut transit time, and diet all affect SCFA synthesis [144]. The breakdown of dietary fiber by the gut microbiota follows three main metabolic routes: hydrolysis, glycolysis, and the pentose-phosphate pathway [145]. The phyla Firmicutes and

Bacteroidetes, making up roughly 70% of total SCFAs [145], with Bacteroidetes mainly producing acetate and propionate, and Firmicutes being the primary sources of butyrate [146].

Acetate, a two-carbon SCFA, is synthesized through the Wood-Wjungdahl and acetyl-CoA pathways by various bacteria, including *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia muciniphila*, *Bacteroides* spp., *Prevotella* spp., *Ruminococcus* spp., and *Streptococcus* spp. [146]. Propionate is produced by species such as *Phascolarctobacterium* spp., *Bacteroides* spp., *Dialister* spp., *Veillonella* spp., *Salmonella* spp., *Roseburia inulinivorans*, *Ruminococcus obeum*, *Megasphaera elsdenii*, and *Coprococcus catus* through the succinate, acrylate, and propanediol pathways [146]. Butyrate is generated by *Roseburia* spp., *Clostridium leptum*, *Eubacterium hallii*, *Coprococcus eutactus*, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Anaerostipes caccae* via the butyryl-CoA: acetate CoA-transferase and phosphotransbutyrylase/butyrate kinase pathways [147].

About 5–10% of the host's energy comes from SCFAs, which are absorbed through the colonic epithelium and enter the hepatic portal circulation [148]. Besides providing energy to the host, SCFAs function as signaling molecules that influence inflammatory responses, systemic blood pressure, and autonomic systems. They inhibit histone deacetylases, alter phagocytosis and chemotaxis, produce reactive oxygen species, promote cell division, and maintain the integrity of the intestinal barrier [148]. For instance, n-butyrate, a four-carbon SCFA, supports aerobic fatty acid oxidation in mitochondria, producing acetyl-CoA for the Krebs cycle [149]. SCFAs also contribute to the synthesis of cholesterol, long-chain fatty acids, and gluconeogenesis [145]. Butyrate influences the expression of claudin 1 (*CLDN1*), mucin genes, and other tight junction proteins vital for intestinal barrier strength [160], is essential for immune balance, reduces endotoxemia and inflammation risks, and lessens adipose tissue activation [150]. An overview of various effects of SCFAs on several organs is shown in Figure 4.

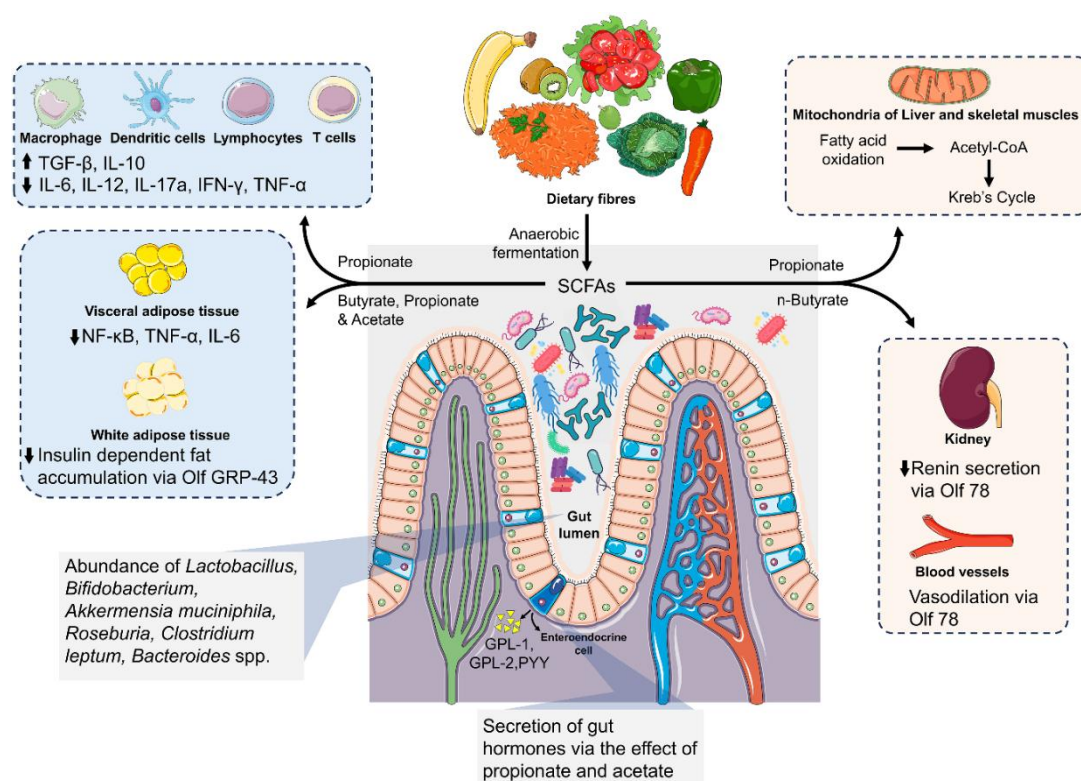


Figure 4. Effect of SCFAs in various organs. SCFAs are derived from the anaerobic fermentation of resistant dietary fibres. In the gut SCFAs positively impact the growth of *Lactobacillus*, *Bifidobacterium*, *Akkermansia muciniphila*, *Roseburia*, *Clostridium leptum*, *Bacteroides* etc. Propionate stimulates macrophages, lymphocytes, T cells, and dendritic cells to increase the secretion of TGF- β and IL-10, while reducing the production of pro-inflammatory cytokines such as IL-6, IL-2, IL-17a, IFN- γ , and TNF- α . Notably, propionate specifically decreases renin secretion and promotes vascular dilation through Olf78. Both propionate and acetate stimulate

enteroendocrine cells to release GLP-1, GLP-2, and PYY. Additionally, n-butyrate serves as a precursor for fatty acid oxidation in the liver and skeletal muscle. Short-chain fatty acids (SCFAs) also inhibit the secretion of NF- κ B, TNF- α , and IL-6 in visceral adipose tissue, while reducing insulin-dependent fat accumulation in white adipose tissue. The Figure illustration was prepared using Servier Medical Art, licensed under a Creative Commons' Attribution 4.0 International license. Bacterial icons were taken from the FLATICONS by FREEPIK (<https://www.flaticon.com/>).

SCFAs are recognized by various free fatty acid receptors (FFARs), including FFAR2 (GPR43), FFAR3 (GPR41), hydroxycarboxylic acid receptor 2 (HCA2, also known as GPR109a), and other G protein-coupled receptors like Olfr-87 in mice and OR51E2 in humans [148,151,152], expressed in different tissues such as white adipose tissue and pancreatic β and α cells. These receptors mediate inflammatory responses and species-specific effects [153]. FFAR signalling is pivotal in modulating immune and inflammatory responses. SCFAs affect cellular functions through receptor activation, intracellular metabolism modulation, and histone deacetylase (HDAC) inhibition [154].

Peptide YY (PYY) and glucagon-like peptide-1 (GLP-1), anorectic hormones secreted by enteroendocrine cells, influence satiety, feeding behaviour, and glucose homeostasis, generally aiding in weight loss and reducing diabetes risk [155,156]. SCFAs prompt the secretion of these hormones [157], enhancing glucose tolerance, boosting intestinal gluconeogenesis, and curbing weight gain [158]. GPR41 activation has been associated with increased production of gut hormones, leptin, and PYY in humans and mice [159], while GPR43 activation in adipocytes reduces insulin-dependent fat accumulation, leading to leaner mice compared to their wild-type counterparts [160]. Furthermore, through its interactions with SCFAs, GPR41 regulates the sympathetic nervous system (SNS), influences a number of physiological processes, and may help explain how diet, probiotics, and prebiotics affect body's homeostasis [161].

SCFAs play a crucial role in reducing blood pressure by inhibiting renin release in the juxtaglomerular apparatus and facilitating relaxation of vascular smooth muscle cells via GPCRs, including olfactory receptor 78 [162]. In models of Dextran sulfate sodium-induced colitis, dietary fiber and SCFAs have been observed to activate GPR43 on colonic epithelial cells. This activation triggers the NLRP3 inflammasome, thereby improving colitis by mediating gut homeostasis through IL-18 [163]. Moreover, SCFAs play a critical role in promoting IL-22 secretion by CD4⁺ T cells and innate lymphoid cells (ILCs) via GPR41 activation and HDAC inhibition. This process enhances the aryl hydrocarbon receptor (AhR) levels and hypoxia-inducible factor 1 α (HIF-1 α). This process helps suppress intestinal inflammation and supports intestinal homeostasis [164]. Neutrophils that do not express GPR43 show an increased movement towards standard chemoattractants and lipopolysaccharides, indicating that a deficiency in SCFA levels could aggravate systemic inflammation by diminishing GPR43-mediated signalling in immune cells [165].

It is well known that SCFAs influence gene expression by directly inhibiting HDACs, which causes histone hyperacetylation [166]. This modification stimulates gene expression by increasing chromatin accessibility [167]. Butyrate and propionate specifically affect both local and systemic immune responses by preserving immunological homeostasis and preventing allergies and autoimmunity through their effects on the intestinal mucosa and lumen [168,169]. SCFAs promote a tolerogenic immune response by inhibiting the expression of co-stimulatory molecules on antigen-presenting cells by blocking HDAC activity and signalling via GPR109A [170]. Additionally, SCFAs support hematopoiesis by promoting the development of dendritic cell precursors that have phagocytic properties but reduced ability to support Th2 cell effector functions, resulting in lower allergic reactions [171]. Butyrate and propionate also promote the acetylation of histones at the Foxp3 locus [172], which supports the thymic production and peripheral conversion of T cells into FoxP3⁺ regulatory T cells [173].

SCFAs modulate T cells, DCs, ILCs, and macrophages. They enhance the production of anti-inflammatory cytokines such as TGF- β and IL-10, while reducing pro-inflammatory cytokines like IL-6, IL-12, IL-17a, IFN- γ , and TNF- α [174]. SCFAs also play a role in decreasing eosinophil

recruitment and allergic cellular infiltration in the airways, thus mitigating inflammation and the IgE antibody response [171].

5.3. Secondary Bile Acids: Metabolism, Signaling, and Immune Modulation

Bile acids (BAs) play a critical role in human health and metabolism. They are initially produced from cholesterol as primary bile acids in the liver, and they circulate between the liver and the colon as part of the enterohepatic system circulation. In the colon, gut microbiota convert primary BAs into secondary BAs via various enzymatic activities, including deconjugation, oxidation, epimerization, dehydroxylation, esterification, and desulfation [175]. The process of deconjugation involves the splitting of glycine and taurine from bile acids by the action of bile salt hydrolase (BSH), an enzyme found in a wide array of bacterial species, including both Gram-positive (e.g., *Bifidobacterium*, *Lactobacillus*, *Clostridium*, *Enterococcus*) and Gram-negative (*Bacteroides*) bacteria [176]. Even certain archaea like *Methanobrevibacter smithii* and *Methanosphaera stadtmanae* possess BSH enzymes that can break down both taurine- and glycine-conjugated bile acids [177].

Bacterial hydroxysteroid dehydrogenase (HSDH) enzymes play a key role in converting primary bile acids, such as cholic acid (CA) and chenodeoxycholic acid (CDCA), into secondary bile acids, including lithocholic acid (LCA) and deoxycholic acid (DCA). This process mainly involves dehydroxylation at the 7 α position. This specific conversion is carried out by a small fraction of anaerobic bacteria belonging to genera like *Bacteroides*, *Clostridium*, *Eubacterium*, *Lactobacillus*, and *Escherichia*, which constitute a minor portion of the gut and colonic microbiota [178]. These anaerobic species represent less than 0.025% of the total gut microbiome and 0.0001% of the colonic microbiota [179]. The majority of these bacteria belong to the *Clostridium* genus, such as *C. hiranonis*, *C. hylemonae*, *C. sordelli*, and *C. scindens* [180]. Furthermore, a fraction of obligate anaerobes belonging to phyla Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes can epimerize bile acids to produce ursodeoxycholic acid (UDCA) in the large intestine [181].

Secondary BAs, especially DCA and LCA, can re-enter the enterohepatic circulation and influence host physiology and disease by activating the nuclear FXR and the G protein-coupled receptor 5 (TGR5) on cell membranes [182]. Besides assisting in nutrient digestion and absorption, bile acids also regulate inflammation, fibrosis, and intestinal barrier function. For instance, FXR activation can maintain intestinal structure and permeability by preventing intestinal ischemia-reperfusion damage [183]. The discovery of BAs' receptors in endothelial cells, fibroblasts, and cardiomyocytes suggested a broader role for bile acids in cardiovascular health, and in treating heart failure caused by gut dysbiosis [184].

The EGFR/Src/ERK signaling pathway can be suppressed by DCA's interaction with FXR at normal levels, lowering the intestinal epithelial cell (IEC) proliferation [185]. Bile acids have been shown to activate the AP-1 and c-Myc signaling pathways, which may also assist in the development and metastasis of colon cancer cells [186]. Furthermore, bile acids can influence enteroendocrine L-cells by activating FXR and TGR5; TGR5 activation increases intracellular cAMP and calcium levels, promoting GLP-1 secretion [187].

TGR5 and FXR, receptors expressed in various immune cells, are notably activated by microbial bile acid derivatives, such as DCA and LCA. Bile acids play an crucial role in regulating the cytokine levels, as evidenced by transcriptomic studies, which show they can lower pro-inflammatory cytokines and chemokines, improve anti-inflammatory responses, promote wound healing, and transform pro-inflammatory macrophages into anti-inflammatory cells [188]. Specifically, LCA is a strong inhibitor of the NLRP3 inflammasome in bone marrow-derived macrophages (BMDMs), blocking caspase-1 maturation and the secretion of IL-1 β and IL-18 via the TGR5-cAMP-PKA pathway. Phosphorylation and ubiquitination of the NLRP3 inflammasome prevent the caspase-1-dependent processing and release of pro-inflammatory cytokines [189]. Moreover, secondary BAs may affect adaptive immunity. For instance, LCA inhibits Th1 cell activation and decreases ERK1/2 phosphorylation by interacting with vitamin D receptor. In both human and mouse T cells,

treatment with secondary BAs decreased STAT1 α/β phosphorylation and Th1-specific cytokine production [190].

5.4. Metabolic Endotoxins and Their Implications in Cardiometabolic Diseases

A well-balanced gut microbiota is vital in maintaining immune and metabolic equilibrium, offering protection against harmful pathogens. Metabolic endotoxins or lipopolysaccharides (LPS) derived from the outer membranes of Gram-negative bacteria are prevalent in the gut [191]. The gut microbiota hosts approximately one trillion bacterial cells, which contribute nearly a gram of LPS within the intestinal lumen. In a dysfunctional gut barrier, gut integrity is compromised and can facilitate the leakage of LPS and other endotoxins into the bloodstream, thereby leading to a range of metabolic issues [192]. An imbalance in the gut microbiota, known as dysbiosis, is associated with an increased risk of cardiometabolic disorders, including hypertension, high cholesterol, and insulin resistance, all of which are significant risk factors for CVD [193]. The difference between a normal gut and a dysbiotic gut is described in Figure 5.

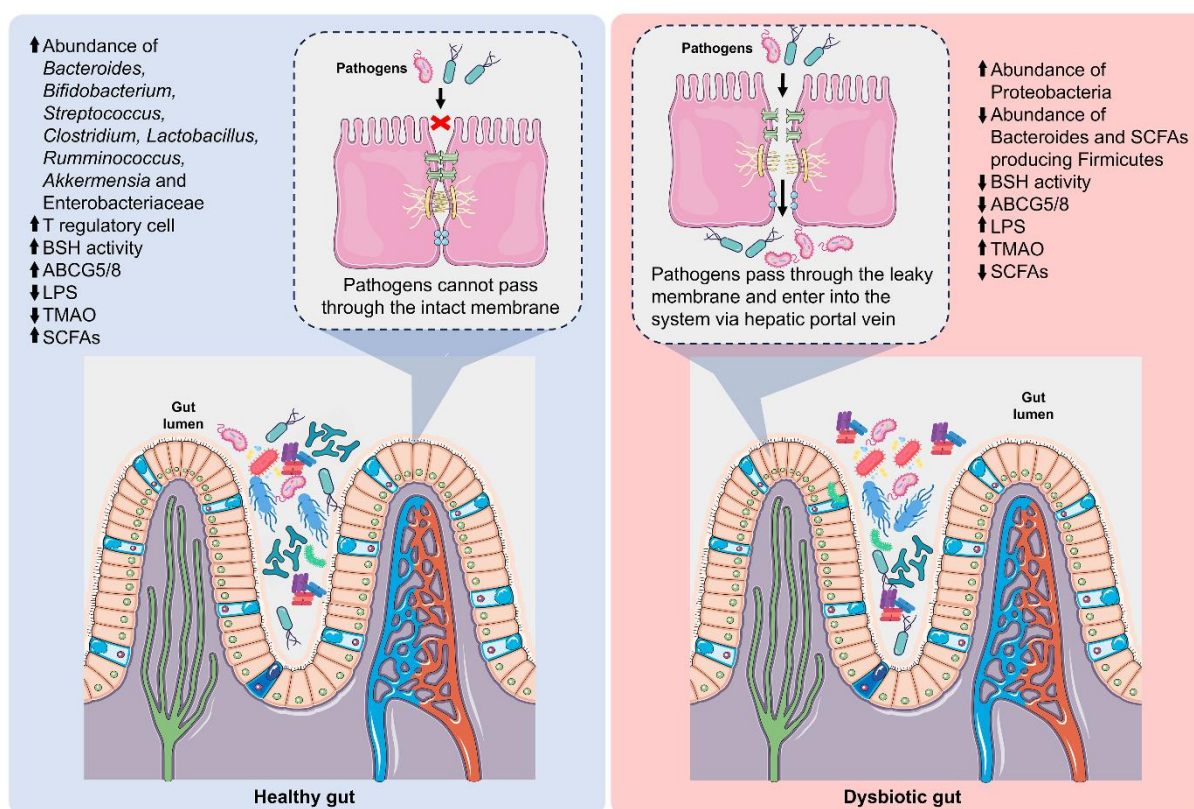


Figure 5. Schematic image showing the difference between the normal gut and the dysbiotic atherosclerotic gut. In a healthy gut, there is an intact tight junction, with a higher abundance of beneficial bacteria, including *Bacteroides*, *Bifidobacterium*, *Streptococcus*, *Clostridium*, *Lactobacillus*, *Ruminococcus*, *Enterococcus*, the *Akkermansia* genus, and the *Enterobacteriaceae* family. Additionally, there is an increased presence of T regulatory cells, BSH activity, ABCG5/8 transporters, and SCFAs, along with lower levels of LPS and TMAO. In contrast, a dysbiotic atherogenic gut is characterized by a reduced abundance of Bacteroidetes and SCFA-producing Firmicutes, decreased BSH activity, ABCG5/8 transporters, T regulatory cells, and SCFAs. It also exhibits an increased abundance of Proteobacteria, higher levels of TMAO, and LPS. The Figure illustration was prepared using Servier Medical Art, licensed under a Creative Commons' Attribution 4.0 International license. Bacterial icons were taken from the FLATICONS by FREEPIK (<https://www.flaticon.com/>).

Characterized by elevated LPS levels in the circulation, which can be two to three times the normal [150], metabolic endotoxemia triggers oxidative stress, harms mitochondrial DNA and

proteins in the heart, increases endothelial cell adhesion molecule expression, and encourages atherosclerosis-promoting activities [194].

Once endotoxins enter the systemic circulation, they bind to carrier molecules such as lipopolysaccharide-binding protein (LBP), bactericidal/permeability-increasing protein (BPI), soluble CD14, or serum lipoproteins, such as HDL and VLDL. LBP aids in extracting LPS from bacterial membranes and prevents the free endotoxins from aggregating in the bloodstream [195]. Complexes of LPS-LBP then bind to CD14 receptors on the surface of innate immune cells such as macrophages, neutrophils, and dendritic cells [196]. This complex transfers the endotoxin to the TLR4/MD2 complex, with the lipid A segment of LPS specifically binding to Toll-like receptor 4 (TLR4) [197]. This interaction activates adapter proteins and kinases, including MyD88, IRAK, TRAF6, NIK, and I κ B, activating NF- κ B [198]. NF- κ B translocates to the nucleus to bind to various gene promoters, initiating the transcription of genes involved in inflammation, including clotting factors, complement proteins, acute phase reactants, cytokines, chemokines, and nitric oxide synthase [199].

Adipocytes expressing TLR4/MD2 complexes rely on soluble CD14 for LPS binding because they lack CD14 receptors on their membranes [150]. Interestingly, even cells lacking TLR4 can respond to LPS [200]. In patients with chronic heart failure (CHF), NF- κ B activity is heightened in leukocytes, with increased expression of TLR2 and TLR4 on circulating monocytes compared to healthy individuals [201–203]. Higher levels of TNF- α , regulated by TLR4, correlate with more severe functional impairments in the Studies of Left Ventricular Dysfunction (SOLVD) trials [204] underscoring the roles of LPS, NF- κ B, and TLR4 in chronic heart failure and positioning endotoxins as potential initiators of inflammation.

It is interesting to note that exposure to LPS can elevate blood insulin and glucose levels and induce weight gain in mice fed a high-fat diet [150]. Research indicates that LPS can cause oxidation of low-density lipoproteins [205]. This condition is implicated by an increase in permeability of the gut and, consequently, elevated circulating LPS levels, which are frequently observed in cardiovascular diseases [206]. Additionally, metabolic endotoxemia is associated with hypertriglyceridemia and the progression of fatty liver disease [207]. Moreover, studies have shown that LPS can increase the activity of endothelial lipase, which lowers the HDL levels [208], and it has been implicated in the development of plaque, progression of atherosclerotic lesions, and the secretion of pro-inflammatory molecules by endothelial cells [209].

6. Therapeutic Strategies Targeting Gut Microbiota-Derived Metabolites for Atherosclerosis

Gut microbiota-derived metabolites, including TMAO, SCFAs, secondary bile acids, and microbial LPS, have been recognized as significant modulators of atherogenesis. These metabolites affect lipid metabolism, vascular inflammation, and immune cell function. As a result, focusing on these metabolites and the related microbial pathways offers a viable supplement to traditional risk-factor management techniques. Broad dietary and lifestyle changes, precise microbiome modulation, and the use of small-molecule inhibitors that target microbial enzymes are examples of therapeutic interventions. The main therapeutic strategies are outlined in this review, along with the suggested mechanisms to reduce atherosclerotic risk and the available evidence supporting their development and clinical assessment.

6.1. Diet and Lifestyle:

Making dietary adjustments is a practical and economical way to affect the gut microbiota's makeup and the metabolites it produces. Diets high in fiber, low in L-carnitine and choline, and high in some polyphenols may improve cardiometabolic health and reduce toxic metabolites. Mechanistically, diet influences the substrates available to microbes, shifts the gut microbial community towards beneficial taxa, and improves the integrity of the intestinal barrier. A diet rich in fresh fruits and vegetables, dietary fibers with fewer animal products, and processed foods can lower

the risk of CVD [210]. Several studies have highlighted the Mediterranean diet (MD) as a potential approach for preventing and reducing the risk of cardiovascular and metabolic diseases [211–213]. The CORDIOPREV trial showed that MD decreased the progression of atherosclerosis in patients with coronary heart disease [214]. Although this diet is rich in nutrients that can generate TMAO, evidence suggests that MD does not affect plasma TMAO concentrations in healthy people [215] or may even reduce them [216–218]. For instance, dietary apigenin has been shown to counteract several pro-atherosclerotic mechanisms associated with TMAO, such as inflammasome activation, low-density lipoprotein uptake, and leukocyte adhesion [219]. The PREDIMED trial revealed that the Mediterranean diet supplemented with extra-virgin olive oil or nuts was associated with a lower incidence of cardiovascular events than the reduced-fat diet. The trial also demonstrated that the Mediterranean diet can reshape the gut microbiota and alter microbial metabolite production, reducing cardiovascular disease risk [220]. Similarly, a study in Australia showed notable differences in the relative abundance of bacterial taxa between individuals following a Mediterranean diet and those following a low-fat diet. An increase in *Butyrococcus* was noted, showing an inverse correlation with changes in systolic blood pressure and significantly contributing to cardiovascular disease outcomes [221].

A cohort study of 307 healthy men using shotgun metagenome and meta-transcriptome analysis of gut microbiota by Ma *et al.* revealed that higher dietary intake shifts the Clostridiales compositions and their ability to utilize the carbohydrate. They also found a significant reduction in C-reactive protein, accompanied by a low or absent *Prevotella copri* population in the gut [222]. Murga-Garrido *et al.* demonstrated that various dietary fibers, including cellulose, inulin, and pectin, modulate the gut microbiota and, in turn, reduce body fat and liver triglyceride levels [223]. In a preclinical study on ApoE^{-/-} knock-out mice, Catry *et al.* reported that a 15-day supplementation with inulin-type fructans (ITFs) improved endothelial function in the arteries of n-3 PUFA-deficient conditions [224]. The results demonstrate the potential of ITFs to promote cardiovascular health, especially in n-3 PUFA-deficient conditions. Likewise, a thorough examination of a randomized controlled clinical trial showed that consumption of isolated triterpene fraction lowers LDL cholesterol levels [225]. Apart from ITFs, beta-glucan supplements have also been shown to lower total LDL cholesterol levels while enhancing endothelial vascular reactivity in healthy individuals [226].

A pre-clinical study on a mouse model has shown that regular exercise increases the concentration of SCFAs [227]. A combination of aerobic and resistance training significantly lowers the prevalence of chronic metabolic disorders. Exercise also enhances gut microbial diversity and nutrient utilization, improves gut barrier function, and modulates neural and hormonal pathways [228]. It has been demonstrated that high-endurance training lowers plasma LPS levels. This implies that exercise might help lower inflammation linked to cardiovascular disease and other metabolic disorders [229]. It is important to note that although exercise benefits the gut microbiota, its effects are short-lived. This emphasizes the necessity for consistent and regular exercise to sustain a constructive impact on the gut microbiota and the associated health benefits [230].

6.2. Natural Product-Based Therapies Targeting Gut Microbiota

Natural products have gained considerable attention in research and are increasingly acknowledged as beneficial complementary therapies in clinical environments. Their diverse chemical compositions and favorable bioavailability contribute to their extensive therapeutic possibilities. Research indicates that natural products can target multiple pathways, making them promising options for preventing and treating atherosclerosis [231]. The natural products therapy of atherosclerosis showed that resveratrol, berberine, curcumin, quercetin, naringin, ginsenoside RC, paeonal, millet shell, polyphenols, flaxseed oil, capsaicin, gastrodia extract, gastrodin, and gypenoside XLIX can delay the progression of atherosclerosis by targeting the gut microbiota and immune cell crosstalk; detailed mechanisms are available elsewhere [232]. Preclinical data reveal that consumption of *Ligustrum robustum* reduces serum TMA and TMAO levels by moderating gut microbiota, increasing fecal cholesterol excretion, decreasing serum and liver cholesterol levels, and

ultimately attenuating diet-induced atherosclerosis [233]. Numerous ongoing and planned clinical trials seek to clarify these compounds' effectiveness and mechanisms. Due to their widespread availability, low toxicity, and extensive immunomodulatory effects, natural products are emerging as promising candidates for treating atherosclerosis. Future pharmaceutical development could benefit from investigating how active natural compounds influence gut microbiota metabolic pathways and assessing whether the resulting metabolites have complementary or opposing effects on atherosclerosis progression. Discovering beneficial metabolites derived from gut microbiota originating from natural products could lead to new strategies for creating innovative therapies to combat atherosclerosis.

6.3. Probiotics

Probiotics are live microorganisms that, when consumed in adequate amounts, provide several health benefits. They are highly regarded in nutraceutical science for their potential health benefit [234]. They have gained considerable attention as potential therapeutics for restoring gut microbial composition and improving cardiovascular health. The abundance of *Lactobacilli* in the gastrointestinal tract can significantly impact the overall well-being of the organism [235]. Probiotics colonized in the gut delay the progression of atherosclerosis by modulating the host's micro-ecology [236]. Qiu *et al.* showed that *L. plantarum* ZDY04 may be a promising strategy for lowering plasma TMAO concentrations and mitigating TMAO-induced atherosclerosis in mice [237]. A randomized, double-blind clinical trial involving 44 patients with coronary artery disease demonstrated that 12 weeks of supplementation with *Lactobacillus rhamnosus* combined with caloric restriction resulted in anti-inflammatory effects and significant weight reduction [238]. Administration of a probiotic containing *Limnosilactobacillus fermentum* on a high-fat diet to Wistar rats restored gut microbial balance associated with improvements in metabolic disturbances and blood pressure abnormalities [239]. Probiotic *Bifidobacterium animalis* subsp. Lactis F1-3-2 intervention can cause a decrease in TMA levels in the cecum of mice and an improvement of lipid metabolism by acting on farnesoid X receptors and cholesterol 7- α hydroxylase [240]. Likewise, *Bifidobacterium breve* Bb4 and *Bifidobacterium longum* strains BL1 and BL7 were found to decrease plasma TMAO and plasma and cecal TMA levels. However, no change in the expression of FMO, FMO3, or FXR proteins, nor in TMAO excretion, was observed [241]. Supplementation with *Lactobacillus fermentum* ZJUIDS06 was shown to elevate colonic SCFA levels and increase the relative abundance of *Parabacteroides* in the cecum of hyperlipidemic hamsters, a key indicator of enhanced SCFA production and improved serum cholesterol profiles [242]. Similarly, *Lactobacillus reuteri* CCFM8631 enhanced acetate, propionate, and butyrate concentrations while reducing fecal TMAO levels in atherosclerosis model mice. This probiotic treatment also modulates the gut microbial environment by elevating the abundance of *Deferribacteres*, Lachnospiraceae NK4A136 group, *Lactobacillus*, and *Dubosiella*, while decreasing *Erysipelatoclostridium* and *Romboutsia* populations [243]. Pham and his team developed a probiotic cocktail using the commercially available *E. coli* Nissle (1917) strain, EcN_TL. They engineered it to continuously produce SCFAs by incorporating the biosynthetic pathways for propionate and butyrate. They observed that the daily intake of EcN_TL markedly reduced myocardial injury and cardiac function. Further analysis elucidated that EcN_TL lessens the neutrophil infiltration into the infarct site and promotes polarization of wound healing macrophages. They also revealed that plasma SCFAs protected the cardiomyocyte from inflammation by suppressing the NF- κ B activation pathway [244]. *Akkermansia muciniphila*, a SCFAs producer, is well known for its probiotic properties and has been associated with regulating glucose, insulin, and leptin [245]. Research into the 16S rRNA gene has identified a reduced presence of *Bacteroides vulgatus* and *Bacteroides dorei* in individuals suffering from CAD. Oral administration of these bacteria into mice prone to atherosclerosis diminished atherosclerotic lesions and mitigated endotoxemia. This is achieved by reducing the production of gut microbial LPS and inhibiting inflammatory immune responses [246]. Although LPS generally has harmful effects, the LPS derived from *Pantoea agglomerans* (LPSp) has demonstrated a capability to decrease LDL cholesterol levels in people with

hyperlipidemia. In ApoE^{-/-} mice on a high-fat diet, LPSp treatment reduced body weight, plasma LDL, and oxidized LDL concentrations, and decreased proinflammatory mediators [247]. Modifying the gut microbiota with probiotic supplements offers a new approach for treating conditions such as coronary artery disease and hyperlipidemia. Ongoing research highlights the potential of probiotics as supportive therapies for cardiovascular health, emphasizing the need for deeper investigation and clinical validation.

6.4. Pharmacological Modulation of the Gut Microbiome in Cardiovascular Disease

Pharmacological interventions can modulate the gut microbiota for cardiovascular health benefits. It is an emerging and promising approach to tackle the atherosclerotic burden. Several drugs and bioactive compounds have shown potential in modulating the composition and functionality of gut microbes, which in turn can influence cardiovascular health. These strategies involve using agents that directly or indirectly target the gut microbiota, including antibiotics, bioactive compounds, and other microbiome-targeted pharmaceuticals.

Metformin, an anti-diabetic drug, minimized the risk of myocardial infarction onset in type 2 diabetes patients in a study to evaluate the risk of all-cause mortality and MACE [258]. Metformin can upregulate glucose uptake in peripheral tissues and regulate the pathway by increasing both plasma and pancreatic levels of GLP-1, the central molecule responsible for SCFA-associated cardioprotective function. It can also reduce the BA absorption by inhibiting the apical sodium-dependent bile acid transporter (ASBT), thereby disrupting the primary BA-mediated FXR activation [259]. A cohort study reveals a significant positive association between metformin and higher abundance of *Akkermensia muciniphila* and SCFAs producers like *Butyrivibrio*, *Bifidobacterium bifidum*, *Megasphaera* [260]. This suggests that metformin not only regulates blood glucose but also promotes a healthier gut microbiome. Acarbose, an alpha-glycosidase inhibitor, is also an alternative to metformin that can upregulate BSH, increase the *Lactobacillus* and *Bifidobacterium* populations, and downregulate the *Bacteroides*, *Alistipes*, and *Clostridium* populations [261]. A preclinical study on the *cutC/D* inhibitor showed that a single dose of Iodomethylcholine (IMC) and Fluoromethylcholine (FMC) significantly reduced TMAO levels for up to 3 days, while minimizing the risk of thrombosis and other significant complications associated with CVD [262]. Meldonium, another TMAO-inhibitory compound, reduces TMAO level by inhibiting L-carnitine metabolism intermediate gamma-butyrobetaine, significantly lowering the *K. pneumoniae* TMAO production [248].

Although antibiotic therapy demonstrated beneficial effects in preclinical studies, several clinical trials reported no significant impact on the disease progression [249]. Conversely, a long-term longitudinal study involving approximately 36,000 adult women revealed that prolonged antibiotic use was linked to an increased risk of cardiovascular disease, likely due to persistent microbiome disturbances, including the loss of beneficial probiotic bacteria [250]. While antibiotics may exhibit short-term benefits in a controlled experimental setup, long-term clinical use could disturb the gut microbiota ecology and expedite cardiovascular risk. This underscores the importance of developing a targeted, narrow therapeutic approach that modulates the gut microbiota without compromising its beneficial functions.

Despite several preclinical and translational studies, the clinical effectiveness and safety of gut microbiota-targeted pharmacotherapies require further validation through large-scale human trials. Future research must integrate multi-omics approaches and precision medicine frameworks to elucidate the interactions among hosts, microbes, and drugs. This understanding will pave the way for personalized microbiome-based therapeutics for the management of cardiovascular diseases.

6.5. Fecal Microbiome Transplantation

Since the US Food and Drug Administration approved fecal microbiome transplantation (FMT) for managing *Clostridioides difficile* infection, it has been used to treat inflammatory bowel disease, irritable bowel syndrome, constipation, metabolic syndrome, and other diseases. Transfer of gut microbiota from lean donors to individuals with metabolic syndrome has been shown to enhance

insulin sensitivity, accompanied by a rise in butyrate-producing bacterial populations, particularly *Roseburia intestinalis* and *Eubacterium hallii* [251]. The therapeutic effect of FMT can be associated with a broader variety of bacteria, viruses, fungi, and archaea that successfully adapt within the recipient's gut, resulting in enhanced functional diversity of the microbiota. FMT can be used to reduce the level of circulating TMAO and the risk of atherosclerosis [252]. In the present scenario, there is a lack of substantial data to establish the effectiveness of fecal microbiota transplantation as a therapeutic for CVD. With the advances in new technology and research, a deeper understanding of the gut microbiota interaction could pave the way for FMT application in promoting cardiovascular health and other systemic conditions.

7. Conclusion

In conclusion, the host microbiota has a complex and significant role in human health. The development of next-generation sequencing (NGS) technologies has further highlighted this fact. These technologies have revealed a wide variety of microorganisms previously impossible to cultivate, underscoring the significant impact of the microbiota on illnesses such as diabetes, Parkinson's disease, Alzheimer's disease, and cardiovascular diseases. The gut microbiota has a multifaceted impact on cardiovascular disease and is crucial for maintaining cardiovascular health. Signalling molecules that control host gut hormones and aid in the liver's synthesis of cholesterol are produced by microbial metabolism in the gut. Some microbial strains produce complex exopolysaccharides and enzymes that may indirectly affect bile acid cleavage or reabsorption, thereby reducing cholesterol levels. However, some gut microbiota components can partake in harmful pathways, transforming beneficial dietary micronutrients into detrimental compounds. Nowadays, artificial intelligence and machine learning (AI-ML) are being used to analyse big data generated from the NGS. Researchers are integrating AI-ML in clinical settings to predict and develop models in response to dietary interventions or probiotic treatments. These prediction models might help clinicians make informed decisions, leading to an optimized cardiovascular health management regime.

Future research must focus on integrating AI-ML and multi-omics data to elucidate the precise mechanisms by which the gut microbiome contributes to health maintenance and CVD development. It should also continue exploring novel strategies, emphasizing the value of combining microbiome data with state-of-the-art technologies to develop tailored, efficient treatments for CVD and other illnesses.

Author Contributions: R.W. conceptualized and designed the study. M.G.S. searched the literature, prepared the first draft, figures, and table. R.W. oversaw the drafting process and critically reviewed the manuscript. All authors reviewed and edited the final draft of the manuscript and collectively approved the final manuscript.

Funding: This study received funding from the Indian Council of Medical Research (ICMR), New Delhi, India, under its Junior Research Fellowship program, awarded to M.G.S. (award grant no.: 3/1/3/JRF-2019/HRD-070(31035)).

Data Availability: No datasets were generated or analysed during the current study.

Acknowledgments: The Council of Scientific and Industrial Research (CSIR), New Delhi, and the CSIR-NEIST, Jorhat, Assam, are gratefully acknowledged for providing the necessary facilities, thereby facilitating the smooth progression of the study. The author would also like to thank the Publication & Intellectual Property Rights Committee, CSIR-NEIST for reviewing and approving this study (manuscript approval No. CSIR-NEIST/PUB/2024/077 Dated: 18-10-2024).

Competing Interests: The authors declare no competing interests.

Abbreviations

CVDs	cardiovascular diseases
WHO	World Health Organization
DALYs	Disability Adjusted Life Years
NCD	non-communicable disease
IHD	ischemic heart disease
SCD	sudden cardiac death
SMC	smooth muscle cell
TMAO	trimethylamine-n-oxide
SCFA	short-chain fatty acid
LPS	lipopolysaccharides
ASCVD	Atherosclerotic cardiovascular disease
LDL	Low-density lipoprotein
oxLDL	Oxidised Low-density lipoprotein
AGEs	advanced glycation-end product
AHA	American Heart Association
GI	gastrointestinal
MWAS	metagenome-wide association
T-RFLP	terminal restriction fragment length polymorphism
CAD	coronary artery disease
LCV	Lymphocystis Virus
TTV	Torque teno virus
VLDL	very low-density lipoprotein
HDL	high-density lipoprotein
Lp(a)	lipoprotein (a)
RCT	Reverse Cholesterol Transport
eNOS	endothelial nitric oxide synthase
TNF- α	tumor necrosis factor- α
IL-1 β	interleukin-1 β
IL-6	interleukin-6
PPAR γ	peroxisome proliferator activator receptor γ
MCP-1	monocyte chemoattractant protein-1
COX-2	cyclooxygenase-2
NF- κ B	nuclear factor κ B
LOX-1	lectin-like oxidised LDL receptor 1
TGF- β 1	transforming growth factor- β 1
VSMCs	vascular smooth muscle cells
MPO	myeloperoxidase
ALEs	advanced lipoxidation end product
MDA	malondialdehyde
4HNE	4-hydroxynonenal
DDAH	dimethyl aminohydrolase
MMP	matrix metalloproteinase
MAPK	mitogen-activated protein kinase
JNK	c-jun N-terminal kinase
VCAM-1	vascular cell adhesion molecule
ICAM	intracellular cell adhesion molecule
Th1	T helper type 1
INF- γ	interferon- γ
GM-CSF	granulocyte macrophage colony-stimulating factor
M-CSF	macrophage colony-stimulating factor
Nrf2	nuclear factor erythroid 2-related factor 2

TLRs	Toll-like receptors
PAMPs	pathogen-associated molecular pattern
DAMPs	damage-associated molecular pattern
MyD88	Myeloid Differentiation Primary Response Gene88
Lp-PLA2	Lipoprotein-associated phospholipase A2
NLRP3	NOD-like receptor 3
NK	natural killer
NKT	natural killer T cells
APC	antigen-presenting cells
DC	dendritic cells
MHC	major histocompatibility complex
T-bet	T-box transcription factor
GATA3	GATA binding protein 3
ROR γ	RARA-related orphan receptor γ
CTLs	cytotoxic T lymphocytes
BCR	B cell receptor
Tfh	T follicular helper
IgG	immunoglobulin G
IgM	immunoglobulin M
GBB	gamma butyrobetaine
TMADH	trimethylamine dehydrogenase
FMO	flavin monooxygenase
FXR	farnesoid X receptor
MACE	major adverse cardiovascular event
HAECs	human aortic endothelial cells
HCAECs	human coronary aortic endothelial cells
CYP7a1	Cholesterol 7 alpha-hydrolase
ABCG5/8	ATP-binding cassette G5/8
NPC1L1	Neimann-Pick C1-like 1
ROS	reactive oxygen species
FHCs	fetal human colon cells
HIV	human immunodeficiency virus
EPCs	endothelial progenitor cells
CLDN1	claudin1
FFARs	free fatty acid receptors
HCA2	hydroxycarboxylic acid receptor 2
HDAC	histone deacetylase
PYY	peptide YY
GLP-1	glucagon-like peptide 1
SNS	sympathetic nervous system
ILCs	innate lymphoid cells
AhR	aryl hydrocarbon receptor
HIF-1 α	hypoxia-inducible factor 1 α
HSDH	hydroxysteroid dehydrogenase
CA	cholic acid
CDCA	chenodeoxycholic acid
LCA	lithocholic acid
DCA	deoxycholic acid
UDCA	ursodeoxycholic acid
IEC	intestinal epithelial cells
cAMP	cyclic adenosine monophosphate

BMDMs	bone marrow-derived macrophages
LBP	lipopolysaccharide-binding protein
BPI	bactericidal/permeability-increasing protein
CHF	chronic heart failure
SOLVD	Studies of Left Ventricular Dysfunction
CORDIOPREV	Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention
PREDIMED	Prevención con dieta Mediterránea
ITF	inulin-type fructans
ASBT	apical sodium-dependent bile acid transporter
IMC	Iodomethylcholine
FMC	Fluoromethylcholine
FMT	fecal microbiome transplantation

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