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Research Progress on the Association Between the Oral–Gut Microbiota Axis and Cardiovascular Disease

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of global mortality despite substantial advances in the pathophysiological understanding and clinical management of this disease. Emerging evidence implicates the oral and intestinal microbiota—two highly complex microbial ecosystems—as critical modulators of cardiovascular homeostasis. These communities are shaped by host immunity, lifestyle, aging, diet, pharmacological agents, and environmental exposure; their dysbiosis has been causally linked to a spectrum of chronic disorders, including CVD. This suggests that the oral and gut microbiota constitute tractable biological targets for CVD intervention. Here, we first delineate the compositional and functional interrelationship between the oral and gut microbiomes. We then summarize mechanistic pathways through which the oral–gut microbiota axis may drive CVD, including (i) direct endothelial invasion, (ii) microbial translocation, (iii) platelet hyperaggregation, (iv) immune-mediated systemic inflammation, and (v) microbial metabolite–host interactions. Finally, we review clinical associations between the oral–gut axis and prevalent CVD phenotypes—atherosclerosis, hypertension, myocardial infarction, and heart failure—and discuss translational perspectives for microbiota-directed therapeutics.

Cardiovascular disease (CVD) is characterized by high morbidity, disability, mortality, and recurrence rates and remains the predominant cause of human death worldwide. According to the World Health Organization (WHO), CVD accounts for approximately 17.9 million deaths annually—32% of all global fatalities []. The relentlessly rising burden imposes formidable socioeconomic and familial strain, underscoring the urgency for effective prevention and control strategies. CVD pathogenesis is multifactorial, arising from intricate interactions among genetic predisposition, environmental exposures, and intrinsic vascular determinants [2]. Although genetic studies have identified numerous heritable risk alleles, mortality has not substantially declined, highlighting the need for alternative, mechanism-based interventions.

The human microbiome—an immense and taxonomically diverse consortium of bacteria, viruses, fungi, and other microorganisms—constitutes an integral extension of the host and has become a focal point in basic, translational, and clinical research [3]. The two largest reservoirs reside within the gastrointestinal tract and the oral cavity. Within the intestinal microbiota, Bacillota, Bacteroidota, Actinomycetota, Fusobacteriota, Pseudomonadota, with Bacteroidetes and Firmicutes comprising > 90% of the community [4]. The oral core

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microbiome comprises the phyla Actinomycetota, Bacteroidota, Bacillota, Fusobacteriota, Pseudomonadota, Saccharibacteria, and Spirochaetota, whose abundance and distribution are maintained in a dynamic equilibrium. [5]. Colonization of the oral cavity is intimately linked to gut microbial succession, as anatomical continuity along the gastrointestinal tract facilitates reciprocal cross talk via the oral–gut, oral–lung, and oral–kidney axes [6]. A balanced oral microbiota competitively excludes pathogens and is indispensable for maintaining oral health [7]. Disruption of the homeostatic balance in microbial abundance or composition predisposes the host to dental caries, periodontitis, and oral malignancies.Crucially, oral microbes can translocate hematogenously and engraft within the gut, thereby establishing an oral–gut microbial axis that contributes to systemic disorders, including but not limited to CVD and chronic obstructive pulmonary disease [8,9]. These observations collectively identify the oral–gut microbiota axis as a tractable biological target for CVD intervention.

Interrelationship Between Oral and Gut Microbiota

Overview of Oral Microbiota

The oral cavity hosts the second-largest microbial community in the human body, surpassed only by that in the gut [10]. Functionally, it serves as an endogenous reservoir that continuously seeds the gastrointestinal tract. Trillions of microorganisms—spanning bacteria, archaea, fungi, protozoa, and viruses—reside in distinct oral niches, existing either as planktonic cells in saliva or as structured biofilms attached to mucosal and dental surfaces. Maintenance of this homeostatic consortium is indispensable for oral health, whereas dysbiosis precipitates pathologies, such as dental caries and periodontitis.

Advances in high-throughput sequencing and multiomics have illuminated the systemic impact of oral microbes, including their emerging role in cardiovascular disease (CVD). To date, 772 distinct prokaryotic species have been catalogued across saliva, the tongue dorsum, the buccal mucosa, the hard palate, supragingival and subgingival plaques, and other sites [11]. These communities initiate food digestion and generate a diverse repertoire of primary and secondary metabolites that can enter the systemic circulation and initiate or amplify systemic inflammation. Clinical and preclinical studies [12,13] have demonstrated that aberrant expansion of Gram-negative anaerobes—exemplified by *Porphyromonas gingivalis*—within dental plaque triggers periodontal inflammation, pocket formation, and loss of tooth attachment. Importantly, periodontal therapy directed at restoring oral microbial equilibrium has been associated with the measurable attenuation of CVD indices, suggesting that modulation of the oral microbiota represents a promising therapeutic avenue.

Oral–Gut Microbiota Axis

The oral cavity and the intestine are anatomically contiguous components of the digestive tract that nurture distinct yet interdependent microbial ecosystems. Comparative metagenomics reveal that ≈45% of bacterial taxa are shared between these two niches, with the phylum Firmicutes, class Clostridia, and order Clostridiales being the most prevalent overlapping taxa [14]. Consequently, perturbations in the oral microbiome can propagate dysbiosis along the gastrointestinal tract, thereby influencing systemic disease trajectories.

Geographic and ethnic heterogeneity further sculpt the oral microbiome: Neisseria predominates in Chinese cohorts, Veillonella in Canadian populations, and Prevotella in Qatari individuals [15,16]. To mitigate such variability in CVD-focused investigations, we propose a three-tier standardization framework: (i) cohort stratification—either region-specific reference databases or globally inclusive, high-powered cohorts stratified by age, sex, and health status; (ii) harmonized sample collection—uniform timing, storage, transport, and metadata acquisition regarding diet, lifestyle, and environment; and (iii) multiomics integration—concomitant profiling of metagenomic, metabolomic, and transcriptomic layers to dissect causal pathways linking microbiota to CVD.

Experimental evidence supports the oral–gut axis as a conduit for microbial translocation. Oral gavage of *Fusobacterium nucleatum* in healthy mice reproducibly alters fecal community composition and increases colonic autophagy markers LC3-I/II, and these effects are reversible with metronidazole [17]. However, most mechanistic insights remain confined to animal models. A recent multinational human study employing high-resolution bioinformatics detected ≈10% of oral taxa—*F. nucleatum* among them—within the gut lumen, substantiating the concept of an oral–gut axis [18,19].

An oral-gut microbiota axis translocation trial was found: 96% of participants (n = 136) harbored 61 shared amplicon sequence variants (ASVs) across oral and fecal compartments. Twenty-six ASVs persisted from childhood to adulthood, indicating lifelong colonization, while overall diversity remained stable until the fifth decade, after which significant shifts occurred. Notably, 62% of shared ASVs exhibited a higher relative abundance in the oral cavity, implicating oral-to-gut translocation as the dominant vector [20]. Collectively, these findings establish the oral–gut microbiota axis as a bidirectional conduit with tangible implications for CVD prevention and treatment.

Mechanistic Impact of the Oral–Gut Microbiota Axis on Cardiovascular Disease

The translocation of oral microbes to the gut is a continuous, multistep process in which a substantial fraction of the oral microbiome can seed and persist within the intestinal tracts of healthy individuals. This oral–gut microbiota axis is now recognized as a bidirectional conduit that can drive cardiovascular pathology through at least five interrelated mechanisms: (i) direct invasion of the vascular endothelium, (ii) microbial translocation and ectopic colonization, (iii) pathogen-induced platelet aggregation, (iv) immune-mediated systemic inflammation, and (v) microbial metabolites. Each pathway represents a potential therapeutic leverage point for CVD.

Endothelial Invasion

Endothelial dysfunction constitutes an early and pivotal event in atherogenesis; it not only fosters plaque formation but also narrows the arterial lumen, thereby restricting blood flow. Poor oral hygiene and overt oral pathology—most notably periodontitis—substantially increase the risk of CVD [21]. Periodontal pathogens can directly invade the cardiovascular system. Upon gaining access to the bloodstream,

they adhere to and transmigrate through endothelial and smooth muscle cells, igniting a robust inflammatory cascade. Critically, even after adjusting for traditional cardiovascular risk factors, individuals with periodontitis exhibit a persistently elevated prevalence of CVD, including coronary artery disease, stroke, myocardial infarction, and atherosclerosis. Roca et al. [22] demonstrated a positive independent association between periodontal disease and incident cardiovascular events. Oral bacteria endowed with pathogenic traits—especially the periodontopathogens—*P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia*—possess the capacity to breach the circulation, subsequently targeting host tissues and disrupting the vascular endothelium [23].

P. gingivalis activates toll-like receptors (TLRs) to elicit the release of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), thereby subverting host immunity while simultaneously propagating systemic inflammation [24]. Moreover, this pathogen triggers the secretion of pro-inflammatory mediators, including TNF, IL-1, IL-6, IL-8, and reactive oxygen species—which, along with microbial metabolites entering the systemic circulation via deglutition or periodontal vasculature, stimulate hepatic production of acute-phase proteins, such as C-reactive protein (CRP), pentraxin-3, and fibrinogen [25–26]. Elevated CRP and fibrinogen, in particular, precipitate endothelial injury, increase blood viscosity, enhance platelet aggregation, and perturb lipid metabolism, collectively narrowing the vascular lumen, reducing blood flow, and markedly elevating the risk of atherogenesis and thrombosis.

Likewise, *T. denticola*, frequently recovered from diseased periodontal pockets, secretes proteases that degrade host extracellular matrix components and immune-effector molecules, thereby amplifying pro-inflammatory cytokine release and provoking endothelial dysfunction that culminates in CVD. *T. forsythia* has similarly been shown to stimulate host immune cells, perpetuate chronic inflammation, and inflict endothelial damage. Collectively, these periodontopathogens—and their virulence factors such as *P. gingivalis* lipopolysaccharide and *T. denticola* proteases—gain hematogenous access, directly injure endothelial cells, and thereby initiate the atherosclerotic process. In summary, periodontal disease is intimately linked to endothelial injury, an obligate precursor of atherosclerosis, underscoring the potential of maintaining optimal oral health as a therapeutic avenue for cardiovascular disease prevention and management.

Microbial Translocation

Microbial translocation enables oral pathogens to disseminate via the bloodstream and ectopically colonize distant tissues, precipitating host dysbiosis and potentially driving chronic disorders, including cardiovascular disease. Oral bacteria readily enter the systemic circulation and elicit low-grade inflammation, a recognized risk factor for atherosclerosis. In one study, *Streptococcus mutans* was detected in every oral sample of C57BL/6J mice and in atherosclerotic plaques, suggesting that this oral commensal turned pathogen may traffic hematogenously to atheromatous lesions and contribute to disease initiation [27]. *P. gingivalis* evades host immune clearance by entering the bloodstream in diverse forms—both free-floating and within leukocytes—via blood and lymphatic vessels and subsequently colonizes the arterial wall. This ectopic colonization directly incites local vascular inflammation and perturbs the lipid profile, accelerating atherosclerotic progression [28]. Once translocated to the gut, *P. gingivalis* disrupts microbial homeostasis by markedly reducing α-diversity and depleting beneficial taxa, such as *Akkermansia* and *Clostridiaceae*; this dysbiosis compromises intestinal barrier integrity and heightens susceptibility to further pathogen colonization [29]. Additionally, *P. gingivalis* induces smooth muscle cell apoptosis and inhibits macrophage efferocytosis [30] while simultaneously impairing endothelial progenitor cell angiogenesis through the Akt/FoxO1 signaling axis, thereby promoting plaque instability and progression [31]. A recent investigation demonstrated the presence of DNA, RNA, and antigens from oral commensals—including *P. gingivalis*, *Actinomyces* spp., and *Veillonella* spp.—within human atherosclerotic lesions, providing direct evidence that translocated oral pathogens participate in disease pathogenesis. As early as 2005, Kozarov et al. [32] recovered viable *P. gingivalis* and *Actinomyces* from primary human coronary endothelial cell cultures established from atherosclerotic tissues, lending robust support to the oral bacterial translocation hypothesis. Furthermore, in apolipoprotein-E–deficient mice inoculated with *P. gingivalis*, administration of metronidazole completely inhibited atherosclerotic lesion development under normal chow conditions and markedly attenuated plaque size and severity under high-fat diet conditions. The underlying mechanism appears to involve an oral–gut microbial axis. Oral dysbiosis increases intestinal permeability, allowing lipopolysaccharide to breach the compromised mucosal barrier and enter the systemic circulation, thereby amplifying bacterial translocation and driving cardiovascular pathology [33].

Platelet Aggregation

Beyond hemostasis, platelets are innate immune sentinel cells that become activated during infection. Oral bacteria can stimulate platelets either directly—via specific bacterial binding and receptor-mediated activation—or indirectly through the release of soluble platelet-activating compounds; reciprocally, platelets are also activated by the host immune response elicited against these microbes. Subsequent platelet aggregation amplifies systemic inflammation and constitutes a mechanistic link to atherogenesis and thromboembolic events.

Viridans streptococci, including *Streptococcus sanguinis*, *S. gordonii*, *S. mutans*, and *S. mitis*, potently induce platelet adhesion and aggregation in vitro. This process is orchestrated by an array of bacterial surface adhesins, such as platelet aggregation–associated protein (PAAP), serine-rich glycoproteins, adhesins, and glucosyltransferases, which collectively facilitate platelet–bacterium interactions.

Fimbriae serve as particularly effective platelet-activating moieties: Fimbriated *P. gingivalis* robustly triggers platelet aggregation in vitro, whereas an isogenic DPG3 mutant lacking major fimbriae fails to do so. Notably, purified fimbriae alone are insufficient to induce aggregation, indicating that additional bacterial factors cooperate with fimbrial structures to elicit full platelet activation [34].

Moreover, the inflammatory milieu generated in response to oral bacteria further primes platelets. Activated platelets promote localized thrombus formation and secrete pro-inflammatory cytokines and chemokines, thereby propagating systemic inflammation and contributing to the pathogenesis of cardiovascular disease.

Immune-Mediated Systemic Inflammation

Dysbiosis of the oral microbiota elicits local and systemic inflammation, perturbs normal cardiovascular and metabolic homeostasis, and accelerates the initiation and progression of CVD. When ecological equilibrium is lost, periodontal pathogens activate neutrophils, macrophages, dendritic cells, and γδ T cells, which in turn release pro-inflammatory cytokines and sustain chronic local inflammation in the periodontium. These inflammatory mediators are further amplified through the oral–gut microbial axis, intensifying systemic inflammation. The resulting elevation of lipopolysaccharide (LPS), pro-inflammatory cytokines (e.g., interleukin-6), and acute-phase reactants (e.g., fibrinogen) fosters atheromatous plaque formation and precipitates chronic disorders, prominently CVD.

LPS, commonly termed endotoxin, is an integral component of the outer membrane of Gram-negative bacteria. Extensive evidence indicates that LPS drives systemic inflammation. Acting as a potent immune modulator, LPS translocates from the oral cavity into the systemic circulation, precipitating endotoxemia and endothelial dysfunction. This translocation proceeds via a well-defined cascade: LPS first binds LPS-binding protein (LBP), the complex then engages membrane-bound or soluble CD14, and, finally, it subsequently signals through toll-like receptor 4 (TLR4). Activation of this cascade triggers an explosive release of pro-inflammatory cytokines, promotes atherosclerotic plaque development, and has been experimentally validated in murine models [35].

Cytokines constitute the pivotal molecular link between the oral microbiota and atherosclerosis. Epidemiological studies employing 16S rRNA gene sequencing have identified robust associations between specific oral taxa and systemic cytokine profiles [36–37]. *P. gingivalis* correlates positively with IL-1β, IL-2, IL-8, and IL-13; *Fusobacterium* spp. correlate with IL-1β; and oral streptococci correlate with a broad spectrum of cytokines (IL-1β, IL-2, IL-4, IL-6, IL-7, IL-9, IL-12, and IL-17). Elevations in IL-1, IL-6, and TNF-α are independently associated with heightened CVD risk, implicating cytokine modulation of the oral microbiota as a potential therapeutic target for CVD prevention.

P. gingivalis, a Gram-negative anaerobe recognized as a keystone pathogen in periodontitis, expresses autoinducers that stimulate oral epithelial cells to secrete IL-8. In concert with IL-6 and monocyte chemoattractant protein-1 (MCP-1), IL-8 promotes endothelial dysfunction, enhances coagulation, increases monocyte adhesion, and upregulates cellular adhesion molecules [38]. *P. gingivalis* and *Fusobacterium nucleatum* further act on macrophages, neutrophils, and monocytes to induce TNF-α, IL-6, and IL-8 production. In a murine model, *P. gingivalis* infection led to the accumulation of macrophages and inflammatory mediators (CD40, IFN-γ, IL-1β, IL-6, and TNF-α) within atherosclerotic lesions; these responses were markedly attenuated in immunodeficient mice [39]. Collectively, these findings establish that dysbiosis-driven immune activation originating in the oral cavity constitutes a critical pathway for the initiation and propagation of cardiovascular disease.

Microbial Metabolites

The oral and gut microbiota exert profound influence over cardiovascular health, with specific taxa and their metabolites mechanistically implicated in the initiation and progression of CVD [40]. Trimethylamine-N-oxide (TMAO) is a paradigmatic gut-derived metabolite that critically modulates CVD risk and outcomes. TMAO originates from dietary precursors rich in trimethylamine—namely choline, L-carnitine, and betaine—which are abundant in fruits, vegetables, nuts, dairy, and red meats. Oral commensals, particularly *Prevotella* and *Fusobacterium* spp., also contribute to TMAO generation. A robust body of evidence demonstrates a positive correlation between circulating TMAO concentrations and both CVD susceptibility and all-cause mortality. TMAO accelerates atherogenesis by eliciting macrophage stress responses that promote foam cell formation, thereby initiating cholesterol-laden plaque development within the arterial walls and ultimately precipitating luminal obstruction. TMAO further impairs reverse cholesterol transport and biliary excretion, leading to progressive cholesterol accumulation in the circulation and heightened atherosclerotic risk [41–42]. Mechanistically, TMAO activates the NOD-like receptor protein 3 (NLRP3) inflammasome in macrophages, provoking the secretion of IL-1β and IL-18, which in turn drive endothelial dysfunction and platelet hyperreactivity. TMAO also upregulates vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on endothelial cells, facilitating leukocyte adhesion and transmigration that underlie plaque formation.

TMAO similarly promotes heart failure (HF) pathogenesis through multiple convergent pathways. Elevated plasma TMAO levels correlate positively with incident and worsening HF. Impaired cardiac perfusion in HF engenders myocardial ischemia and increases intestinal permeability, permitting bacterial translocation and systemic entry of deleterious metabolites, such as TMAO. Endothelial NLRP3 inflammasome activation (with downstream release of IL-1β, IL-6, and TNF-α) promotes vascular calcification and endothelial dysfunction, thereby exacerbating HF. TMAO also perturbs calcium signaling, adversely affecting platelet function and myocardial contractility. Furthermore, elevated TMAO is associated with an increased risk of atrial fibrillation and ventricular arrhythmias [43]. Experimental data indicate that TMAO modifies cardiomyocyte electrophysiology by altering the action potential duration and calcium handling, leading to a predisposition to arrhythmogenesis [44].

Short-chain fatty acids (SCFAs) are pivotal microbial metabolites that regulate gluconeogenesis, lipid metabolism, and inflammatory tone. Oral taxa—*Streptococcus*, *Actinomyces*, *Lactobacillus*, *Propionibacterium*, and *Prevotella*—harbor carbohydrate-active enzymes that ferment dietary carbohydrates to SCFAs, thereby sustaining host energy homeostasis. High-sugar dietary patterns markedly modulate the oral microbiota and SCFA output. The cardiovascular effects of oral-derived SCFAs remain incompletely resolved, with studies yielding apparently contradictory findings. SCFAs exert systemic anti-inflammatory effects via inhibition of NF-κB and Akt signaling, reduced production of pro-inflammatory cytokines, histone deacetylase inhibition, and activation of G-protein-coupled receptors, collectively conferring cardiovascular protection [45]. Conversely, SCFAs can modulate the expression of junctional and adhesion proteins, potentially compromising oral epithelial integrity while simultaneously exerting systemic anti-inflammatory effects that may improve cardiovascular outcomes [46].

Nitric oxide (NO) is a bioactive gaseous transmitter that induces vasodilation, suppresses inflammation, lowers blood

pressure, and preserves endothelial integrity, thereby preventing CVD. Its circulating levels are closely correlated with CVD risk, rendering NO a valuable biomarker for cardiovascular events. Recent evidence [47] underscores the critical role that oral microbiota play in regulating systemic NO bioavailability. Oral bacteria generate substantial amounts of NO, serving as an auxiliary reservoir that compensates for insufficient endogenous NO synthase (NOS) activity. When endogenous NOS-derived NO is limiting, oral microbes metabolize salivary nitrite to NO, thereby maintaining vascular homeostasis. Consequently, compositional or functional perturbations of the oral microbiota can significantly alter systemic NO levels and modulate CVD risk. Delineating the mechanistic links between oral microbial NO metabolism and cardiovascular health may inform novel diagnostic and therapeutic strategies.

Hydrogen sulfide (H_2S) is an endogenous gaseous signaling molecule that, at low physiological concentrations, exerts cytoprotective, antioxidant, anti-inflammatory, antihypertensive, and antiatherogenic effects. Paradoxically, elevated oral H_2S levels correlate with local inflammatory exacerbation. Oral bacteria with proteolytic activity catabolize sulfur-containing amino acids to generate H_2S, the principal malodorous compound in halitosis; therefore, oral H_2S concentration is routinely employed as a biomarker of halitosis and as a metric for assessing therapeutic efficacy [48]. Studies have demonstrated [49] that oral H_2S levels remain low in healthy individuals but increase markedly in patients with oral disease, reflecting a higher pathogen burden. Consequently, oral-derived H_2S may influence systemic H_2S pools and modulate cardiovascular outcomes. Clarifying this relationship is essential for a comprehensive understanding of H_2S-mediated cardiovascular protection.

Association Between the Oral-Gut Axis and Cardiovascular Disease

The oral and gut microbiota are now recognized as integral regulators of cardiometabolic health. Emerging evidence demonstrates that bidirectional interactions within the oral-gut axis critically modulate the initiation and progression of cardiovascular disorders, including hypertension, dyslipidemia, atherosclerosis, and coronary heart disease.

Hypertension

Hypertension impairs vascular function and causes target-organ damage in the heart, kidneys, and brain, which is often accompanied by metabolic dysfunction, insulin resistance, and dyslipidemia [50–53]. The oral–gut axis contributes to blood pressure regulation; specific taxa—*P. gingivalis*, *Prevotella* spp., and *Veillonella* spp.—are potent inducers of pro-inflammatory cytokines and are significantly associated with hypertension. *P. gingivalis* activates endothelial cells, causing them to release angiotensin II and inflammatory mediators, thus amplifying vascular inflammation and arterial hypertension [54]. *Prevotella* and *Veillonella* disrupt nitric oxide homeostasis, whereas *Rothia* and *Neisseria* support vascular function via the nitrate–nitrite–nitric oxide pathway.

The compositional overlap between oral and gut microbiota in hypertensive subjects suggests microbial translocation and colonization [55]. Saliva-derived *Veillonella* can ectopically colonize the intestine and exacerbate hypertension, providing direct evidence of oral–gut cross talk [56]. Compared with normotensive controls, hypertensive individuals exhibit reduced gut microbial richness and alpha diversity, with an expansion of *Prevotella* [57]. Obesity-related essential hypertension is linked to alterations in both oral and gut microbiota and to elevated systemic pro-inflammatory cytokines, implying that microbial interactions drive blood pressure elevation via systemic inflammation [58]. Correlations between the microbiota and plasma metabolites such as sphingosine-1-phosphate (S1P) indicate that microbial modulation of S1P-related pathways may influence blood pressure [59]. Additionally, the gut microbiota–derived metabolite TMAO augments angiotensin II–induced vasoconstriction, further linking the oral–gut axis to hypertension [60]. Because intestinal sodium absorption is governed by gut microbiota, dysbiosis can alter salt handling and thereby affect blood pressure. In hypertensive rats fed a high-salt diet, the abundance of Enterobacteriaceae and Corynebacteriaceae increased, whereas that of anaerobic Clostridia decreased, indicating microbial involvement in blood pressure regulation [61]. High salt intake also reduces *Bacteroides fragilis* and elevates cortisol, leading to increased blood pressure [62]. Collectively, these findings position the oral–gut axis as a novel therapeutic target for hypertension.

Dyslipidemia

Dyslipidemia is a key driver of cardiometabolic disease and is intimately linked to dysbiosis of the oral–gut microbiota [63]. Periodontitis patients with dysbiosis exhibit decreased high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL) and triglycerides. Periodontal pathogens, their metabolites, and associated pro-inflammatory cytokines contribute to lipid disturbances and lipid peroxidation [64].

Compared with healthy controls, hyperlipidemic mice with periodontitis display pronounced gut dysbiosis characterized by heightened inflammation and impaired intestinal barrier function. Nonsurgical periodontal therapy restores gut microbial composition, reestablishes barrier integrity, and ameliorates systemic lipid derangements, underscoring the importance of the oral–gut axis in dyslipidemia [65]. Gut dysbiosis can induce oxidative stress, activate the NLRP3 inflammasome, and trigger systemic inflammation, culminating in endothelial dysfunction and dysregulated glucose–lipid metabolism [66]. A study found that germ-free mice fed a high-fat diet accumulate less fat but excrete more lipids in their feces, thereby altering cholesterol metabolism [67]. Compared with colonization by "lean" microbiota, the transplantation of "obese" microbiota into germ-free mice promotes whole-body fat accumulation, highlighting the causal role of the microbiota in lipid homeostasis [68].

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease and a leading cause of cardiometabolic disorders. Oral bacteria readily enter the systemic circulation and incite low-grade inflammation, a cardinal risk factor for atherosclerosis [69]. *S. mutans* was detected in all oral samples and in atherosclerotic plaques, suggesting the hematogenous dissemination of oral bacteria to atheromatous lesions [70]. *P. gingivalis* evades host immunity, enters the bloodstream via blood and lymphatic vessels, and colonizes the arterial wall, thereby

inducing local vascular inflammation and perturbing lipid profiles to promote atherosclerotic progression [71].

Streptococci dominate the oral cavity, and the increased intestinal abundance of streptococci correlates with coronary atherosclerosis and systemic inflammatory markers [72]. *S. mutans* promotes atherosclerosis by adhering to type I collagen, inducing platelet aggregation, invading endothelial cells, and augmenting IL-6, MCP-1, and foam cell formation. Oral *Fusobacterium nucleatum* alters endothelial surface marker expression and modulates vascular endothelial growth factor receptor signaling, impairing neovascularization during inflammation. This bacterium also promotes intestinal inflammation via TLR4/NF-κB activation, amplifying systemic inflammation and accelerating atherosclerosis [73]. Salivary detection of gut-associated oral species, such as *Streptococcus anginosus* and *S. parasanguinis*, underscores their association with poor dental health and coronary atherosclerosis [74]. A murine study revealed that the gut microbiota mediates the proatherogenic effects of chronic apical periodontitis in $ApoE^{-/-}$ mice [75].

Periodontitis, the most prevalent oral inflammatory disease, is characterized by the progressive destruction of gingival connective tissue, periodontal ligament, and alveolar bone. Dental plaque biofilms composed of viridans streptococci initiate periodontitis, whereas anaerobes (*P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia*) sustain chronic disease. Periodontitis serves as a microbial reservoir; these organisms can translocate across ulcerated gingival epithelium into the bloodstream, affecting adjacent gingival microcirculation. The magnitude of bacteremia in periodontitis patients correlates directly with gingival inflammation severity. Large-scale meta-analyses [76, 77] and a prospective US-based study [78] indicate that periodontitis significantly increases the risk of peripheral and carotid atherosclerosis. Bacterial DNA from 23 distinct oral commensals has been identified in atherosclerotic plaques harvested from 1,791 individuals undergoing interventional procedures. Moreover, viable *P. gingivalis* and *Aggregatibacter actinomycetemcomitans* have been cultured from primary human coronary endothelial cells isolated from atherosclerotic tissues, demonstrating that periodontal pathogens can translocate to vascular smooth muscle and cardiac endothelial cells, thereby initiating cardiovascular pathology [79, 80].

Coronary Heart Disease

Coronary heart disease (CHD) represents the cumulative endpoint of metabolic dysregulation and is intimately associated with the disruption of the oral–gut microbiota axis [81]. Dysbiosis impairs host metabolic function, attenuates immune regulation, compromises barrier defenses, and amplifies systemic inflammation and metabolic dysfunction—key drivers of CHD initiation and progression [82]. Microbial translocation is a critical trigger: Pathogens can migrate via intestinal, hematogenous, or immune routes, precipitating gut dysbiosis [83]. The resultant barrier dysfunction permits translocated oral bacteria and their metabolites to enter the systemic circulation, activate host immunity, stimulate proinflammatory cytokine release, disrupt glucose and lipid metabolism, exacerbate endothelial injury and atherogenesis, and thereby accelerate CHD [84, 85]. This translocation-mediated pathology is amplified in the context of concomitant metabolic disorders, such as dyslipidemia and diabetes, establishing a vicious cycle.

The microbial metabolite TMAO exacerbates oxidative stress by reducing superoxide dismutase activity while increasing malondialdehyde and glutathione peroxidase levels, thereby accelerating endothelial senescence and vascular aging [86]. The microbiota-derived metabolite N,N,N-trimethyl-5-aminovaleric acid impairs fatty acid oxidation by inhibiting carnitine synthesis, thus promoting cardiac hypertrophy [87]. Imidazole propionate activates the p62/mTORC1 pathway in hepatocytes and cardiomyocytes, enhancing insulin resistance and promoting myocardial injury [88, 89].

Conclusions and Perspectives

Cardiovascular disease remains the leading global cause of morbidity and mortality; consequently, effective prevention and intervention are critical imperatives for public health. The intricate interplay among the human microbiota, the host, and the external environment is essential for maintaining systemic homeostasis. The microbiota provides the host with nutritional support, immune education, and colonization resistance, while the host offers adhesive and colonization niches. The external environment constitutes the ecological substrate upon which both the host and its associated microbiota depend for survival. Perturbation of any component in this triad can act as a key driver of chronic disorders, including cardiovascular disease (CVD).

The oral–gut microbiota axis has emerged as a novel research frontier, and accumulating evidence emphasizes its pivotal role in cardiometabolic health. In this review, we delineate the bidirectional interactions between oral and gut microbes, detail mechanistic pathways through which the oral–gut axis influences CVD development, and summarize its associations with common cardiovascular conditions. Nevertheless, our current understanding is far from complete. The vast microbial diversity of the oral cavity and gastrointestinal tract, together with the metabolic complexity of the host, leaves the mechanistic links between the axis and CVD largely unresolved. Most existing studies are cross-sectional, providing only static snapshots that constrain causal inference. Moreover, investigations often treat oral and gut communities in isolation rather than as an integrated axis, and many rely on animal models that inadequately recapitulate human microbial contributions to disease.

Future research should therefore prioritize the elucidation of molecular mechanisms operating along the oral–gut microbiota axis, the identification of key microbial metabolites and signaling pathways in humans, and the implementation of longitudinal designs that track axis dynamics and their impact on CVD. Specifically, four strategic directions are proposed. (i) Large-scale, prospective clinical and interventional cohorts should be employed to trace temporal changes in oral microbiota that precede or accompany cardiovascular events, thereby clarifying causal relationships between the oral–gut axis and CVD. (ii) Integrated multiomics platforms (metagenomics, metaproteomics, and metabolomics) should be combined with in vitro and in vivo disease models to dissect functional and structural alterations along the axis, map species-level distributions, and uncover the molecular circuitry linking microbial communities to CVD pathogenesis. (iii) Systems biology approaches should leverage high-dimensional axis data to develop predictive models for early CVD

detection and risk stratification, enabling timely preventive interventions. (iv) Therapeutic strategies that modulate the oral microbiota—implemented as adjuncts to periodontal therapy—should be personalized according to individual microbial signatures. Such precision interventions promise to optimize efficacy, minimize adverse effects, and realize the concept of "comanagement of chronic diseases" by simultaneously targeting oral pathology and cardiovascular risk.

In summary, the oral–gut microbiota axis offers a transformative perspective for improving cardiometabolic health. Rigorous mechanistic clarification is required before its full clinical potential can be realized.

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