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Alzheimer's Disease

The Oral-Brain Axis in Alzheimer's Disease: Mechanisms Linking Periodontitis to Neurodegeneration and Translational Prevention Strategies

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Abstract

Alzheimer's disease (AD) is characterized by extracellular amyloid-β (Aβ) deposition, intracellular tau pathology, neuroinflammation, and progressive neurodegeneration. Increasing evidence suggests that chronic peripheral inflammatory conditions may influence the onset and progression of AD. Periodontitis, a dysbiosis-driven inflammatory disease of the tooth-supporting tissues, has emerged as a potential contributor through systemic immune activation, recurrent bacteremia, and dissemination of microbial virulence factors.

This narrative review selectively synthesizes foundational and recent peer-reviewed human observational, neuropathologic, experimental, and interventional studies identified through targeted literature searches and citation chaining; studies were prioritized for direct mechanistic or translational relevance to the oral–brain axis. Epidemiologic studies report associations of periodontal disease with cognitive decline, dementia, and cerebral amyloid burden, whereas experimental work supports biologically plausible pathways involving systemic inflammation, blood–brain barrier dysfunction, neuroglial activation, amyloid and tau signaling, gingipain-mediated neurotoxicity, oxidative stress, extracellular vesicles, vascular dysfunction, and oral–gut–brain interactions.

Current evidence supports association and biologic plausibility more strongly than causation. No randomized trial has demonstrated that periodontal therapy prevents cognitive decline or AD, and the phase 2/3 GAIN trial of the gingipain inhibitor atuzaginstat did not meet its co-primary cognitive or functional endpoints. Periodontal prevention and treatment should be recommended for their established oral and general-health benefits; whether they alter AD incidence or progression remains unproven.

Keywords: Alzheimer's disease; Periodontitis; Oral microbiome; Porphyromonas gingivalis; neuroinflammation; Blood-brain barrier; Gingipains; Prevention

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INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of dementia and is currently conceptualized as a biologically defined disorder characterized by amyloid-β (Aβ) deposition, tau pathology, neurodegeneration, and progressive cognitive decline (Jack et al., 2018; Long & Holtzman, 2019). Although the traditional focus of AD research has centered on intrinsic brain pathology, increasing evidence suggests that systemic inflammatory and vascular processes contribute to disease initiation and progression (DeTure & Dickson, 2019; Heneka et al., 2015; Jack et al., 2018; Long & Holtzman, 2019). Neuroinflammation, blood-brain barrier (BBB) dysfunction, and altered innate immune signaling are now recognized as integral components of AD pathophysiology rather than secondary consequences of amyloid accumulation alone (DeTure & Dickson, 2019; Heneka et al., 2015; Long & Holtzman, 2019).

Periodontitis is a chronic inflammatory disease initiated by dysbiotic microbial biofilms and characterized by progressive destruction of the tooth-supporting tissues. In addition to local tissue damage, periodontitis produces persistent systemic inflammatory signaling, recurrent bacteremia, and dissemination of microbial virulence factors into the circulation (Dewhirst et al., 2010; Hajishengallis & Chavakis, 2021). These processes have been implicated in several chronic systemic conditions, including atherosclerotic cardiovascular disease, diabetes mellitus, and adverse pregnancy outcomes, suggesting that the biological effects of periodontal inflammation extend well beyond the oral cavity (Hajishengallis & Chavakis, 2021; Landers et al., 2025).

Interest in a potential oral–brain axis has grown substantially over the past decade. Epidemiologic studies have associated periodontal disease with cognitive decline, dementia, and incident AD, while neuroimaging studies have reported increased cerebral amyloid burden among individuals with greater periodontal disease severity (Ide et al., 2016; Kamer et al., 2015; Noble et al., 2014; Sparks Stein et al., 2012). In parallel, experimental investigations have demonstrated that oral exposure to periodontal pathogens can induce neuroinflammation, amyloid accumulation, BBB dysfunction, and cognitive impairment in animal models (Dominy et al., 2019; Ilievski et al., 2018; Kong et al., 2025). Particular attention has focused on Porphyromonas gingivalis, a keystone periodontal pathogen whose DNA, lipopolysaccharide, and gingipain proteases have been identified in AD brain tissue and linked to AD-like pathology in experimental systems (Dominy et al., 2019; Ilievski et al., 2018; Poole et al., 2013).

Although current evidence remains insufficient to establish a direct causal relationship, the convergence of epidemiologic, neuropathologic, and mechanistic findings supports a biologically plausible connection between chronic periodontal inflammation and neurodegenerative disease (Hajishengallis & Chavakis, 2021; Ilievski et al., 2018; Kong et al., 2025; Poole et al., 2013). Importantly, periodontitis represents a potentially modifiable exposure. As discussed in the authors' recent review of oral health as a determinant of Alzheimer's disease, interventions that reduce periodontal inflammation and improve oral microbial homeostasis may offer practical opportunities to lessen systemic inflammatory burden while broader questions of causality continue to be investigated (Landers et al., 2025).

This review examines the principal mechanisms through which periodontitis may contribute to AD pathogenesis, including systemic inflammation, microbial dissemination, BBB dysfunction, microglial activation, amyloidogenesis, tau-related pathology, gingipain neurotoxicity, vascular injury, and synaptic dysfunction. Particular emphasis is placed on translational prevention strategies that may be implemented in clinical practice despite the absence of definitive dementia-prevention trials. The proposed oral–brain axis is summarized in Figure 1, which illustrates how periodontal inflammation and microbial dissemination converge on neurovascular, neuroimmune, amyloidogenic, tau-related, and synaptic pathways relevant to AD.

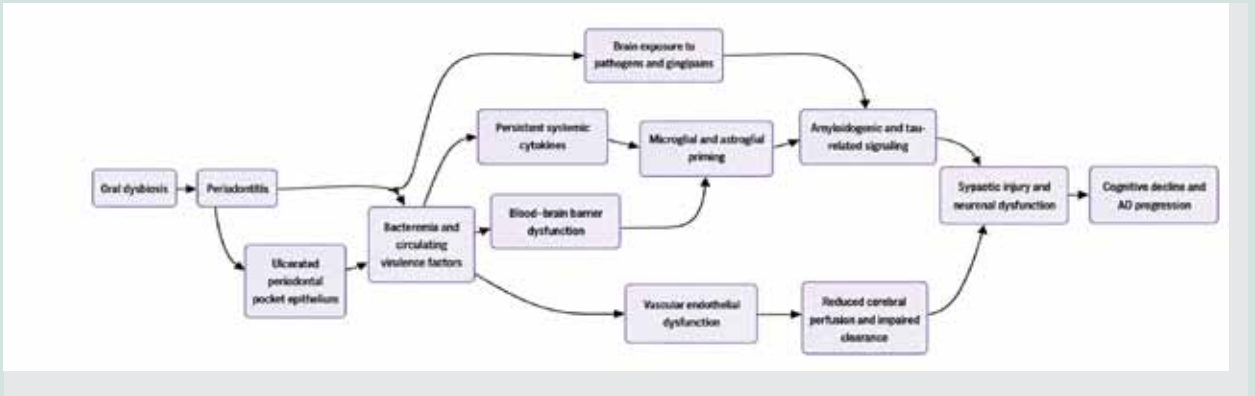

Figure 1: Mechanistic pathways linking periodontitis to neurodegeneration. The schematic depicts hypothesized routes by which oral dysbiosis and periodontitis may generate persistent systemic cytokine signaling, bacteremia and circulating virulence factors, blood–brain barrier dysfunction, microglial and astroglial priming, vascular endothelial dysfunction, impaired cerebral perfusion and clearance, amyloidogenic and tau-related signaling, synaptic injury, and cognitive decline. Arrows indicate proposed biologic relationships rather than proven causal pathways. AD, Alzheimer's disease. Figure constructed by the authors from evidence synthesized in Hajishengallis and Chavakis (2021), Dominy et al. (2019), Sweeney et al. (2018), Ising et al. (2019), and Sanz et al. (2020).

SYSTEMIC INFLAMMATION

The most extensively supported mechanism linking periodontitis and Alzheimer's disease is chronic systemic inflammation. Periodontitis is characterized by persistent activation of the host immune response, resulting in elevated circulating concentrations of pro-inflammatory mediators including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), C-reactive protein, and other acute-phase reactants (Hajishengallis & Chavakis, 2021; Landers et al., 2025). Unlike transient inflammatory responses, periodontal inflammation may persist for years, creating a sustained low-grade inflammatory state capable of influencing distant organ systems.

This systemic inflammatory burden is particularly relevant to AD because neuroinflammation is now recognized as a central component of disease pathogenesis rather than a secondary response to amyloid deposition. Activated microglia and astrocytes contribute to neuronal dysfunction through production of cytokines, reactive oxygen species, and inflammasome-mediated signaling pathways that amplify both amyloid and tau pathology (Heneka et al., 2015; Ising et al., 2019). Peripheral inflammatory signals derived from chronic periodontal disease may therefore interact with pre-existing neurodegenerative processes by promoting microglial priming, endothelial activation, and altered neuroimmune homeostasis.

A useful framework is to view periodontitis as a chronic inflammatory amplifier rather than a solitary cause of AD. In this model, repeated exposure to periodontal inflammatory mediators lowers the threshold at which age-related, genetic, vascular, and metabolic risk factors become clinically consequential. This interpretation is consistent with contemporary models of AD that emphasize interactions among amyloid biology, innate immunity, vascular dysfunction, and systemic inflammatory exposures (DeTure & Dickson, 2019; Heneka et al., 2015; Jack et al., 2018; Long & Holtzman, 2019).

Importantly, this mechanism is supported by both biological plausibility and clinical evidence. Individuals with periodontal disease demonstrate elevated systemic inflammatory markers, while observational studies have associated periodontal inflammation with cognitive decline and incident AD (Ide et al., 2016; Noble et al., 2014; Sparks Stein et al., 2012). Although causality remains unproven, chronic periodontal inflammation represents one of the most biologically plausible pathways through which oral disease may contribute to neurodegenerative risk (Hajishengallis & Chavakis, 2021; Landers et al., 2025).

HEMATOGENOUS DISSEMINATION OF PERIODONTAL PATHOGENS AND VIRULENCE FACTORS

A second major mechanism linking periodontitis and Alzheimer's disease involves the systemic dissemination of periodontal pathogens and their virulence products. The ulcerated epithelium lining periodontal pockets provides a large vascular interface through which microorganisms, endotoxins, proteases, and bacterial nucleic acids can enter the circulation. Consequently, transient bacteremia may occur during routine activities such as mastication, flossing, and toothbrushing in individuals with active periodontal disease (Hajishengallis & Chavakis, 2021; Landers et al., 2025).

Among periodontal pathogens, Porphyromonas gingivalis has received the greatest attention because of its established role in periodontal dysbiosis and its potential neurotropic properties. While periodontitis is a polymicrobial disease, P. gingivalis functions as a keystone pathogen capable of disrupting host immune regulation and promoting a pathogenic microbial community (Hajishengallis & Chavakis, 2021; Singhrao & Olsen, 2019). Experimental studies have demonstrated that chronic oral exposure to P. gingivalis can result in brain colonization, neuroinflammation, amyloid accumulation, and cognitive impairment in animal models (Dominy et al., 2019; Ilievski et al., 2018).

Evidence supporting dissemination to the central nervous system is strengthened by neuropathologic investigations. Poole et al. (2013) identified periodontopathic virulence factors in postmortem AD brain tissue, while Dominy et al. (2019) reported the presence of P. gingivalis DNA and gingipain antigens in brains from individuals with AD. Furthermore, elevated serum antibodies directed against periodontal pathogens have been associated with incident AD and cognitive decline, suggesting that chronic exposure to periodontal microorganisms may precede overt neurodegenerative disease (Ide et al., 2016; Noble et al., 2014; Sparks Stein et al., 2012).

These observations do not establish direct causation and must be interpreted cautiously. Detection of microbial components within AD-relevant tissues cannot exclude the possibility of secondary colonization or other confounding factors. Nevertheless, the convergence of epidemiologic, neuropathologic, and experimental evidence substantially strengthens the biologic plausibility of an oral–brain axis. Rather than functioning as a singular causative agent, P. gingivalis and related periodontal pathogens may act as chronic microbial stressors that amplify neuroinflammation, vascular dysfunction, and proteinopathy in susceptible individuals (Landers et al., 2025; Poole et al., 2013; Singhrao & Olsen, 2019).

Importantly, this dissemination model extends beyond intact bacterial invasion. Circulating lipopolysaccharides, gingipains, extracellular vesicles, and other virulence factors may exert biologic effects even when viable organisms are absent. This broader perspective helps reconcile the variability observed across human studies and suggests that microbial signaling, rather than persistent infection alone, may represent the most clinically relevant aspect of the periodontal–AD relationship (Landers et al., 2025; Poole et al., 2013; Singhrao & Olsen, 2019).

BLOOD-BRAIN BARRIER DYSFUNCTION

The Blood–brain Barrier (BBB) is a highly specialized neurovascular interface that regulates the movement of cells, proteins, metabolites, and microbial products between the systemic circulation and the central nervous system. Increasing evidence indicates that BBB dysfunction is an early event in cognitive decline and Alzheimer's disease, particularly among individuals with vascular risk factors and APOE4-associated susceptibility (Bell et al.,

2012; Liu et al., 2013; Montagne et al., 2020; Sweeney et al., 2018). Consequently, any chronic systemic condition capable of impairing BBB integrity may have important implications for neurodegenerative disease progression.

Periodontitis may contribute to BBB dysfunction through both inflammatory and microbial mechanisms. Chronic periodontal inflammation is associated with sustained elevations in circulating cytokines, including IL-1β, IL-6, and TNF-α, which can promote endothelial activation and disrupt tight-junction integrity within the neurovascular unit (Hajishengallis & Chavakis, 2021; Sweeney et al., 2018). Experimental studies further suggest that periodontal virulence factors, particularly lipopolysaccharide and gingipain proteases produced by Porphyromonas gingivalis, may directly alter key junctional proteins such as occludin and claudin-5, increasing barrier permeability and facilitating entry of inflammatory mediators into the brain (Dominy et al., 2019; Landers et al., 2025).

The significance of BBB dysfunction extends beyond microbial access. A compromised barrier also impairs the brain's ability to maintain immune homeostasis and efficiently clear toxic metabolites, including amyloid-β. Sweeney et al. (2018) described BBB breakdown as a common feature of multiple neurodegenerative disorders, while Montagne et al. (2020) demonstrated that BBB dysfunction can precede cognitive decline in cognitively normal individuals carrying the APOE4 genotype. These findings support the view that BBB impairment is not merely a consequence of neurodegeneration but may actively contribute to disease progression.

Within the context of the oral–brain axis, chronic periodontal exposure may represent an additional source of neurovascular stress superimposed upon age-related, vascular, and genetic vulnerabilities. Repeated inflammatory signaling, transient bacteremia, and exposure to circulating virulence factors could gradually erode BBB integrity, thereby amplifying downstream neuroinflammatory and amyloidogenic processes. Although direct human evidence remains limited, the convergence of vascular biology, experimental periodontology, and AD research provides a compelling rationale for considering BBB dysfunction as a central mechanistic link between oral disease and neurodegeneration (Dominy et al., 2019; Hajishengallis & Chavakis, 2021; Landers et al., 2025; Montagne et al., 2020; Sweeney et al., 2018).

Importantly, this mechanism reinforces the broader concept that periodontitis is unlikely to influence AD through a single pathway. Rather, BBB dysfunction may serve as a critical point of convergence through which systemic inflammation, microbial dissemination, vascular injury, and impaired protein clearance interact to accelerate disease-relevant pathology.

AMYLOIDOGENESIS

Accumulation of amyloid-β (Aβ) remains a defining feature of Alzheimer's disease and occupies a central position within contemporary models of disease pathogenesis (Jack et al., 2018; Long & Holtzman, 2019). Although amyloid deposition alone does not fully explain cognitive decline, substantial evidence indicates that Aβ biology is closely linked to innate immunity, chronic inflammation, and host-defense responses. This relationship has prompted growing interest in the possibility that persistent peripheral infections, including periodontitis, may influence amyloidogenic signaling pathways (Heneka et al., 2015; Long & Holtzman, 2019).

Several mechanisms have been proposed to explain this association. Chronic periodontal inflammation increases systemic cytokine production and innate immune activation, both of which may alter amyloid precursor protein processing and promote Aβ accumulation (Hajishengallis & Chavakis, 2021; Heneka et al., 2015). In addition, experimental evidence suggests that Aβ may function in part as an antimicrobial peptide, raising the possibility that sustained exposure to microbial pathogens could stimulate amyloid production as a component of the host-defense response (Long & Holtzman, 2019).

Animal studies provide some of the strongest support for this concept. Ilievski et al. (2018) demonstrated that chronic oral exposure to Porphyromonas gingivalis resulted in brain colonization, increased neuroinflammation, and elevated Aβ production in wild-type mice. More recently, Kong et al. (2025) reported that periodontitis-induced neuroinflammation activated the IFITM3–Aβ signaling axis, producing AD-like neuropathology and cognitive decline in experimental models. Together, these studies suggest that chronic periodontal inflammation may promote a cerebral environment favorable to amyloid accumulation.

Human evidence remains more limited but is nevertheless suggestive. In cognitively normal older adults, periodontal disease has been associated with greater cerebral amyloid burden on positron emission tomography imaging, supporting a potential relationship between oral inflammatory status and amyloid deposition in vivo (Kamer et al., 2015). Neuropathologic studies identifying P. gingivalis DNA and gingipain antigens within AD brain tissue further support the possibility that chronic microbial exposure contributes to amyloid-related pathology, although such findings do not establish causation (Dominy et al., 2019; Poole et al., 2013).

The most defensible interpretation of the current literature is that periodontitis may function as an amyloidogenic amplifier rather than an independent initiator of AD pathology. Chronic oral inflammation is unlikely to account for amyloid deposition in isolation; however, it may interact with genetic susceptibility, aging, vascular dysfunction, and innate immune activation to accelerate amyloid accumulation and downstream neurodegenerative processes. This view is consistent with contemporary multifactorial models of AD and aligns with the broader oral–brain framework proposed throughout this review (Hajishengallis & Chavakis, 2021; Landers et al., 2025; Long & Holtzman, 2019).

TAU PATHOLOGY

Although amyloid-β deposition remains a defining feature of Alzheimer's disease, the burden and distribution of tau pathology correlate more closely with neuronal dysfunction, cognitive decline, and disease severity (Ising et al., 2019; Jack et al., 2018; Long & Holtzman, 2019). Consequently, understanding factors that influence tau phosphorylation, aggregation, and propagation is critical when evaluating potential modifiers of AD progression.

Several mechanisms associated with periodontitis may

affect tau biology. Chronic periodontal inflammation promotes sustained production of pro-inflammatory cytokines, oxidative stress, and innate immune activation, all of which can influence intracellular signaling pathways involved in tau phosphorylation (Hajishengallis & Chavakis, 2021; Heneka et al., 2015). Experimental studies have demonstrated that inflammatory mediators can activate kinases such as glycogen synthase kinase-3β (GSK-3β) and other tau-relevant signaling pathways, thereby increasing the likelihood of abnormal tau modification and aggregation (Heneka et al., 2015; Ising et al., 2019).

Recent animal studies provide additional support for this relationship. Kong and colleagues demonstrated that periodontitis-induced neuroinflammation activated the IFITM3–Aβ pathway and was accompanied by AD-like neuropathologic changes, including alterations in tau-related signaling (Kong et al., 2025). Likewise, chronic oral exposure to Porphyromonas gingivalis has been associated with neuroinflammation, neuronal injury, and molecular changes consistent with accelerated neurodegenerative processes (Dominy et al., 2019; Ilievski et al., 2018). While these findings do not establish direct induction of tauopathy, they suggest that chronic periodontal inflammation may create a cerebral environment favorable to tau dysregulation.

Inflammasome biology provides another plausible mechanistic bridge. Ising et al. (2019) demonstrated that activation of the NLRP3 inflammasome promotes tau pathology and disease progression in experimental models of AD. Because periodontal disease is characterized by persistent activation of innate immune and inflammasome-associated pathways, chronic oral inflammation may contribute indirectly to tau propagation through sustained neuroimmune stimulation (Hajishengallis & Chavakis, 2021; Heneka et al., 2015; Ising et al., 2019).

Importantly, the current human evidence remains indirect. No study has definitively demonstrated that periodontitis independently causes neurofibrillary tangle formation in humans. The stronger conclusion is that periodontal disease may amplify upstream processes known to influence tau pathology, including neuroinflammation, oxidative stress, microglial activation, vascular dysfunction, and impaired protein homeostasis. Within a multifactorial model of AD, these effects could accelerate disease progression without serving as the primary initiating event (Heneka et al., 2015; Ising et al., 2019; Long & Holtzman, 2019).

From a translational perspective, the significance of this mechanism lies in its convergence with other pathways described throughout this review. The same periodontal exposures that promote systemic inflammation, BBB dysfunction, and amyloidogenesis may simultaneously enhance tau-relevant signaling. Such convergence reinforces the concept that periodontitis functions as a chronic biologic stressor capable of influencing multiple components of AD pathology rather than a single isolated molecular target.

GINGIPAIN NEUROTOXICITY

Among the proposed molecular links between periodontitis and Alzheimer's disease, gingipains have emerged as perhaps the most compelling and extensively studied candidates. Gingipains are cysteine proteases secreted by Porphyromonas gingivalis that play essential roles in nutrient acquisition, immune evasion, biofilm persistence, and periodontal tissue destruction (Dominy et al., 2019; Poole et al., 2013; Singhrao & Olsen, 2019). Their potential significance in AD arises from their ability to influence inflammatory signaling, disrupt host protein function, and exert direct neurotoxic effects.

Interest in gingipains intensified following the work of Dominy et al. (2019), who identified gingipain antigens in postmortem AD brain tissue and reported associations with tau pathology and neurodegeneration. In the same study, pharmacologic inhibition of gingipains reduced bacterial burden, attenuated neuroinflammatory changes, and improved markers of neuronal health in experimental models. These findings generated considerable interest because they provided a mechanistically coherent pathway linking a specific periodontal virulence factor to several hallmark features of AD pathology.

Several biologic mechanisms have been proposed. Gingipains can degrade structural and regulatory host proteins, disrupt immune signaling pathways, promote inflammatory cytokine production, and impair barrier integrity (Dominy et al., 2019; Singhrao & Olsen, 2019). Experimental studies further suggest that gingipains may contribute to neuronal injury through effects on synaptic proteins, tau-relevant pathways, and cellular homeostasis. Because these proteases can be released independently of intact bacterial cells, their biologic impact may extend beyond direct microbial invasion and may help explain how periodontal dysbiosis influences distant tissues, including the brain.

The presence of gingipains within AD-relevant tissues also provides an important conceptual bridge between microbial exposure and neurodegeneration. Earlier neuropathologic investigations identified periodontopathic virulence factors in postmortem AD brains, supporting the possibility that chronic oral infection may leave detectable molecular signatures within the central nervous system (Poole et al., 2013). Although such findings do not establish that gingipains initiate AD pathology, they strengthen the plausibility of a biologic connection between periodontal disease and neurodegenerative processes.

Despite these observations, important limitations remain. Detection of gingipains in human tissue does not prove causation, and independent replication of some findings has been limited. Furthermore, it remains unclear whether gingipains function as primary drivers of pathology, secondary amplifiers of existing disease, or biomarkers of broader microbial dysbiosis (Dominy et al., 2019; Singhrao & Olsen, 2019). Consequently, the current evidence is best interpreted as demonstrating a highly plausible mechanistic pathway rather than definitive proof of disease causation.

Nevertheless, gingipain biology remains highly relevant to the oral–brain axis hypothesis because it provides a specific molecular mechanism capable of linking periodontal infection to neuroinflammation, BBB dysfunction, tau-relevant signaling, and neuronal injury. Unlike broader inflammatory models, which rely on indirect systemic effects, gingipains represent a discrete and biologically testable target that may help clarify the

contribution of periodontal disease to AD pathogenesis in future translational and interventional studies (Dominy et al., 2019; Landers et al., 2025; Singhrao & Olsen, 2019).

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION

Oxidative stress represents a common downstream pathway through which chronic periodontal inflammation may contribute to neurodegenerative injury. Both periodontitis and Alzheimer's disease are characterized by excessive production of reactive oxygen species (ROS), impaired antioxidant defenses, and disruption of cellular bioenergetics (Hajishengallis & Chavakis, 2021; Heneka et al., 2015; Long & Holtzman, 2019). Although oxidative stress is unlikely to function as the primary link between oral disease and AD, it may amplify the effects of inflammation, vascular dysfunction, and microbial exposure on vulnerable neural tissues.

Periodontal inflammation promotes oxidative stress through sustained activation of neutrophils, macrophages, and other immune cells that generate ROS as part of the host-defense response (Hajishengallis & Chavakis, 2021). While these mechanisms are protective during acute infection, chronic activation can result in cumulative oxidative damage to proteins, lipids, nucleic acids, and cellular membranes. Systemically, this contributes to endothelial dysfunction and inflammatory signaling; within the central nervous system, similar processes have been implicated in neuronal injury and progressive neurodegeneration (Heneka et al., 2015; Long & Holtzman, 2019).

Mitochondria are particularly susceptible to oxidative injury because of their central role in cellular energy production. Mitochondrial dysfunction has long been recognized as a feature of AD and contributes to impaired neuronal metabolism, reduced synaptic resilience, and increased vulnerability to protein aggregation (Long & Holtzman, 2019). Chronic systemic inflammation associated with periodontitis may further exacerbate these abnormalities by increasing oxidative burden and promoting metabolic stress within the neurovascular and neuroimmune systems.

Importantly, oxidative stress should not be viewed as an isolated mechanism. Rather, it serves as a point of convergence for several pathways discussed throughout this review. Systemic inflammation, microglial activation, blood-brain barrier dysfunction, vascular injury, and microbial virulence factors all contribute to oxidative imbalance, which in turn amplifies neuronal dysfunction and accelerates disease progression. This convergence may help explain why periodontitis is associated with a broad spectrum of AD-relevant pathologies despite the absence of a single dominant causal pathway (Hajishengallis & Chavakis, 2021; Heneka et al., 2015; Landers et al., 2025; Long & Holtzman, 2019).

From a translational perspective, recognition of oxidative stress as a shared downstream mechanism reinforces the rationale for reducing chronic periodontal inflammation. Although antioxidant therapies have produced mixed results in AD, interventions that decrease persistent inflammatory and microbial stimuli may indirectly reduce oxidative burden and improve systemic biologic resilience (Landers et al., 2025).

EXTRACELLULAR VESICLES AS EMERGING MEDIATORS OF THE ORAL-BRAIN AXIS

Extracellular vesicles (EVs), including bacterial outer membrane vesicles (OMVs), have emerged as a potentially important mechanism through which periodontal pathogens may exert effects beyond the oral cavity. Unlike whole bacterial cells, EVs are nanoscale structures capable of transporting biologically active cargo including lipopolysaccharides, proteases, adhesins, nucleic acids, and other virulence factors to distant tissues (Landers et al., 2025; Singhrao & Olsen, 2019). Because of their small size and stability, EVs may facilitate systemic dissemination of pathogenic signals even when viable microorganisms are not detectable.

Within the context of periodontal disease, Porphyromonas gingivalis produces OMVs that retain many of the virulence characteristics of the parent organism, including gingipain-associated activity (Singhrao & Olsen, 2019). Experimental studies suggest that these vesicles can interact with endothelial and immune cells, modulate inflammatory signaling pathways, and contribute to tissue injury at sites remote from the oral cavity. Such findings provide a biologically plausible explanation for how periodontal dysbiosis may influence distant organs without requiring sustained bacteremia or direct microbial invasion.

The potential relevance of EVs to Alzheimer's disease lies in their ability to bridge several mechanisms discussed throughout this review. By transporting inflammatory and microbial cargo, vesicles may contribute to endothelial dysfunction, blood-brain barrier disruption, microglial activation, and amplification of neuroinflammatory signaling (Landers et al., 2025; Singhrao & Olsen, 2019). Consequently, EVs represent a conceptual link between local oral infection and systemic neuroimmune effects.

At present, however, the precise contribution of extracellular vesicles to human AD remains uncertain. Most evidence derives from in vitro studies, animal models, or mechanistic investigations rather than prospective clinical studies. Therefore, EV-mediated signaling should be regarded as an emerging component of the oral–brain axis rather than a fully established pathogenic pathway. Future research will be needed to determine whether vesicle-associated biomarkers, microbial cargo, or gingipain-containing OMVs contribute meaningfully to disease progression in humans.

Despite these limitations, extracellular vesicles remain an important area of investigation because they offer a mechanistically coherent explanation for how periodontal pathogens may influence neural tissues without persistent colonization of the brain itself. As understanding of vesicle biology advances, this pathway may help clarify several unresolved questions regarding the relationship between chronic oral infection and neurodegeneration.

GUT-BRAIN AXIS PERTURBATION

Growing evidence suggests that interactions between the intestinal microbiome and the central nervous system influence neuroinflammation, amyloid biology, and neurodegenerative disease progression. This concept, commonly referred to as the gut–brain axis, has generated

interest in the possibility that chronic periodontal disease may affect brain health indirectly through alterations in gastrointestinal microbial ecology (Harach et al., 2017; Long & Holtzman, 2019; Singhrao & Olsen, 2019).

The oral cavity serves as a major source of microorganisms entering the gastrointestinal tract, with billions of oral bacteria swallowed each day. In the setting of periodontal dysbiosis, changes in oral microbial composition may influence downstream gut microbial communities, host immune responses, and metabolite production (Hajishengallis & Chavakis, 2021; Landers et al., 2025). Although the precise mechanisms remain incompletely understood, alterations in gut microbiota have been associated with systemic inflammation, impaired barrier function, and changes in immune signaling pathways relevant to AD pathogenesis (Harach et al., 2017; Long & Holtzman, 2019).

Experimental studies provide support for this broader framework. Harach and colleagues demonstrated that the absence of gut microbiota reduced cerebral amyloid pathology in transgenic mouse models of AD, highlighting the potential influence of microbial ecosystems on disease progression (Harach et al., 2017). While these findings do not specifically implicate periodontal disease, they suggest that microbial communities outside the brain can influence neurodegenerative processes through immune and metabolic mechanisms.

At present, evidence directly linking periodontal disease, gut dysbiosis, and AD remains limited. The most reasonable interpretation is that oral–gut interactions may function as an adjunctive pathway that complements other mechanisms described in this review, including systemic inflammation, vascular dysfunction, and microbial dissemination. Rather than representing a primary explanation for the periodontal–AD association, gut–brain signaling may contribute additional inflammatory and metabolic stress within a broader network of interacting biologic processes (Hajishengallis & Chavakis, 2021; Landers et al., 2025; Singhrao & Olsen, 2019).

Future studies integrating oral microbiome profiling, gut microbial analysis, and AD biomarkers will be necessary to determine the relative importance of this pathway. Until such data become available, the gut–brain axis should be regarded as a promising but still emerging component of the oral–brain framework.

VASCULAR MECHANISMS

Vascular dysfunction represents one of the most biologically plausible pathways through which periodontitis may influence Alzheimer's disease progression. Increasing evidence suggests that AD is not solely a disorder of amyloid and tau accumulation but also a disease of neurovascular dysfunction, impaired cerebral perfusion, and compromised blood-brain barrier integrity (Montagne et al., 2020; Sanz et al., 2020; Sweeney et al., 2018). Consequently, chronic conditions that adversely affect vascular health may contribute to cognitive decline through mechanisms that extend beyond traditional neurodegenerative pathways.

Periodontitis has long been associated with systemic endothelial dysfunction, accelerated atherosclerosis, and increased cardiovascular risk (Hajishengallis & Chavakis, 2021; Huang et al., 2023; Sanz et al., 2020). Persistent periodontal inflammation promotes production of pro-inflammatory cytokines, acute-phase reactants, oxidative stress, and endothelial activation, all of which contribute to vascular injury (Dominy et al., 2019; Hajishengallis & Chavakis, 2021; Sanz et al., 2020). These effects are not confined to the oral cavity; rather, they reflect a systemic inflammatory burden capable of influencing vascular beds throughout the body, including the cerebral circulation.

The relationship between vascular dysfunction and AD is particularly relevant because cerebral blood flow plays a critical role in maintaining neuronal health, nutrient delivery, metabolic waste clearance, and blood-brain barrier function (Montagne et al., 2020; Sweeney et al., 2018). Chronic reductions in vascular efficiency may impair clearance of amyloid-β, increase susceptibility to ischemic injury, and exacerbate neuroinflammatory processes. In this context, periodontal disease may contribute to a neurovascular environment that is less resilient to age-related and neurodegenerative stressors.

Evidence supporting this connection extends beyond theoretical plausibility. Consensus reports and systematic reviews have identified an independent association between periodontitis and cardiovascular disease involving endothelial dysfunction and atherogenesis (Sanz et al., 2020). Likewise, neurovascular dysfunction is increasingly recognized as an early feature of AD, particularly among individuals with vascular risk factors and APOE4-associated susceptibility (Montagne et al., 2020; Sweeney et al., 2018). These observations suggest that vascular injury may represent an important point of convergence between periodontal disease and neurodegeneration.

Importantly, the vascular pathway complements rather than competes with the inflammatory and microbial mechanisms discussed elsewhere in this review. Chronic periodontal inflammation may simultaneously promote endothelial dysfunction, impair blood-brain barrier integrity, amplify systemic inflammatory signaling, and reduce cerebral perfusion. Together, these effects create conditions that favor neurodegenerative progression even in the absence of direct microbial invasion of neural tissue.

The translational implications of this mechanism are substantial. Unlike many proposed molecular pathways in AD, vascular health is a clinically actionable target. Effective periodontal treatment has been associated with improvements in systemic inflammatory markers and endothelial function, suggesting that oral health interventions may influence broader vascular biology (Hajishengallis & Chavakis, 2021; Landers et al., 2025; Sanz et al., 2020). Although direct evidence that periodontal therapy reduces dementia risk is not yet available, the established relationship between periodontal disease and cardiovascular health provides a strong rationale for considering periodontal management as part of a comprehensive brain-health strategy.

SYNAPTIC DYSFUNCTION: THE FINAL COMMON PATHWAY

Although Alzheimer's disease is traditionally defined by amyloid plaques and neurofibrillary tangles, cognitive impairment correlates most closely with synaptic dysfunction and neuronal loss (DeTure & Dickson, 2019;

Jack et al., 2018; Long & Holtzman, 2019). Synapses are the functional units through which neurons communicate, and their progressive deterioration represents a critical determinant of memory impairment, executive dysfunction, and declining cognitive performance. Consequently, any factor capable of accelerating synaptic injury may influence the clinical expression and progression of AD.

The oral–brain mechanisms discussed throughout this review converge at this level. Chronic systemic inflammation, microglial activation, blood-brain barrier dysfunction, vascular compromise, oxidative stress, amyloid accumulation, tau pathology, and microbial virulence factors each contribute to conditions that impair synaptic integrity (Dominy et al., 2019; Hajishengallis & Chavakis, 2021; Heneka et al., 2015; Ising et al., 2019; Landers et al., 2025; Long & Holtzman, 2019). While no single pathway fully explains the relationship between periodontitis and AD, their combined effects create a biologic environment characterized by persistent neuroinflammation, reduced neuronal resilience, and impaired cellular homeostasis.

Microglia play a particularly important role in this process. In healthy brains, microglia participate in synaptic maintenance, remodeling, and clearance of damaged cellular components. Under chronic inflammatory conditions, however, activated microglia may become maladaptive, promoting excessive synaptic pruning, inflammatory signaling, and neuronal injury (Heneka et al., 2015; Ising et al., 2019). Periodontal disease, through its sustained inflammatory and microbial burden, may contribute to this shift toward a chronically activated neuroimmune state.

Vascular dysfunction provides a complementary mechanism. Adequate cerebral perfusion is essential for maintaining synaptic activity, metabolic function, and neuronal survival. Periodontitis-associated endothelial dysfunction and systemic vascular inflammation may reduce the brain's ability to meet these demands, particularly in aging individuals already vulnerable to neurodegenerative change (Montagne et al., 2020; Sanz et al., 2020; Sweeney et al., 2018). Simultaneously, impaired blood-brain barrier function and altered amyloid clearance further compromise neuronal homeostasis.

Experimental studies support this systems-level perspective. Animal models of chronic periodontal infection demonstrate neuroinflammation, neuronal injury, and cognitive impairment that extend beyond isolated amyloid or tau changes (Dominy et al., 2019; Ilievski et al., 2018; Kong et al., 2025). These findings suggest that periodontal disease may influence multiple interconnected pathways that ultimately converge on synaptic dysfunction, the

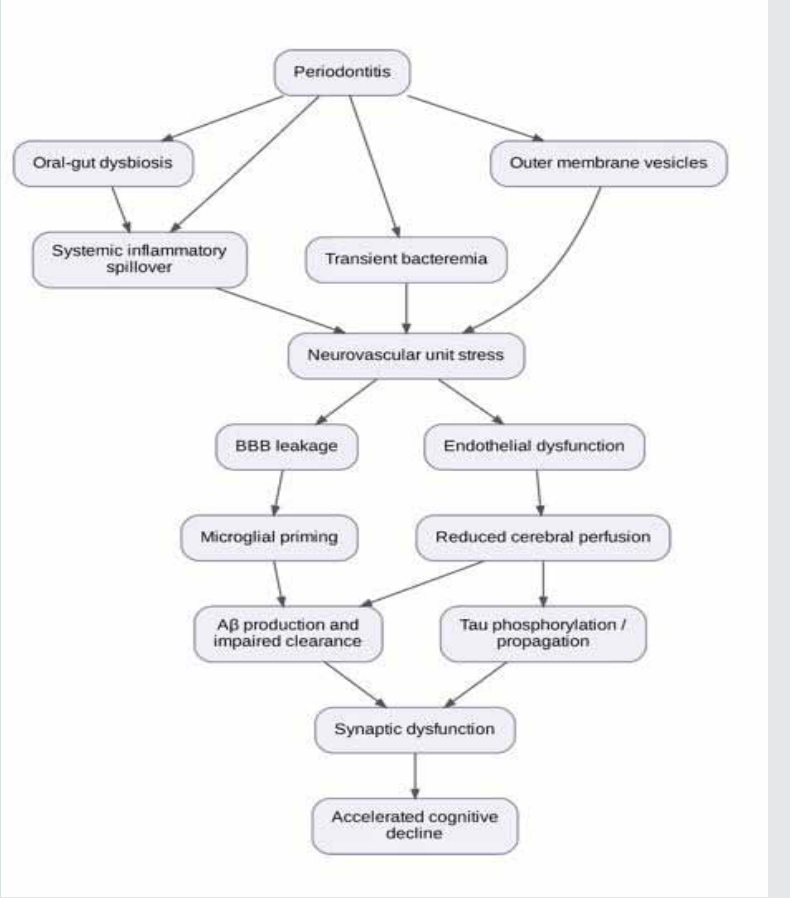

Figure 2: Interactions contributing to neurodegeneration. The schematic summarizes a hypothesized reinforcing network linking periodontitis and oral–gut dysbiosis to systemic inflammatory spillover, transient bacteremia, outer membrane vesicles, neurovascular-unit stress, blood–brain barrier leakage, endothelial dysfunction, microglial priming, reduced cerebral perfusion, amyloid-β production and impaired clearance, tau phosphorylation and propagation, synaptic dysfunction, and accelerated cognitive decline. Arrows indicate proposed mechanistic relationships and do not establish causality. Aβ, amyloid-β; BBB, blood–brain barrier. Figure constructed by the authors from evidence synthesized in Long and Holtzman (2019), Hajishengallis and Chavakis (2021), Harach et al. (2017), Dominy et al. (2019), Sweeney et al. (2018), and Kong et al. (2025).

pathologic process most directly linked to cognitive decline.

From an analytic standpoint, this convergence may explain why periodontitis remains associated with AD across diverse study designs despite variability in specific microbial findings and mechanistic interpretations. The significance of periodontal disease may not depend on a single pathway being universally present. Rather, chronic oral inflammation may exert cumulative effects across several biologic systems that collectively reduce neural resilience and accelerate progression toward cognitive impairment.

This perspective also provides a useful framework for prevention. If periodontitis contributes to neurodegeneration through multiple overlapping mechanisms, then reducing chronic periodontal inflammation may offer benefits that extend beyond any individual molecular target. Such an approach aligns with contemporary models of AD prevention, which emphasize management of established modifiable risk factors across the lifespan (Landers et al., 2025). Figure 2 demonstrates how these interactions are not independent but operate as a reinforcing network in which inflammatory, vascular, microbial, and neurodegenerative processes amplify one another.

ACTIONABLE PREVENTION AND RISK-REDUCTION STRATEGIES

A major challenge in translating oral–brain research into clinical practice is the absence of definitive evidence that periodontal treatment prevents Alzheimer's disease. Nevertheless, the convergence of epidemiologic, mechanistic, and systemic-health literature supports a pragmatic approach in which management of periodontal inflammation is viewed as a low-risk component of broader brain-health strategy (Hajishengallis & Chavakis, 2021; Landers et al., 2025; Sanz et al., 2020). Importantly, the rationale for intervention does not depend on proving that periodontitis directly causes AD. Rather, it is based on the recognition that chronic oral inflammation contributes to systemic inflammatory, vascular, and microbial exposures that overlap substantially with pathways implicated in neurodegeneration.

PERIODONTAL THERAPY

The most evidence-supported intervention is comprehensive periodontal treatment, including scaling and root planing followed by supportive periodontal maintenance. Periodontal therapy reduces periodontal pocket depth, bleeding on probing, microbial burden, and local inflammatory activity while also improving systemic inflammatory markers and endothelial function (Hajishengallis & Chavakis, 2021; Landers et al., 2025; Sanz et al., 2020). Because many of the proposed oral–brain mechanisms originate within chronically inflamed periodontal tissues, treatment of active periodontitis represents the most rational strategy for reducing potential downstream neurologic consequences.

At present, no randomized clinical trial has demonstrated that periodontal therapy prevents cognitive decline or AD. However, given its established benefits for oral and systemic health, treatment of periodontitis should be encouraged irrespective of future dementia outcomes. Within the oral–brain framework, periodontal therapy is best viewed as an intervention that targets a potentially modifiable source of chronic inflammatory burden rather than a proven anti-dementia treatment (Landers et al., 2025).

INTERDENTAL PLAQUE CONTROL

Daily interdental cleaning is an important adjunct to toothbrushing because interproximal surfaces are inadequately cleaned by brushing alone. Evidence from network meta-analyses demonstrates that flossing, interdental brushes, and oral irrigation devices can reduce gingival inflammation and improve periodontal outcomes when used consistently (Kotsakis et al., 2018). Reduction of plaque accumulation at these sites decreases gingival bleeding, microbial load, and chronic inflammatory exposure.

For individuals at elevated risk of neurodegenerative disease, interdental cleaning should be regarded as a simple and accessible strategy for limiting one of the principal drivers of periodontal inflammation. Although AD-specific evidence is lacking, maintenance of periodontal health remains consistent with broader goals of reducing systemic inflammatory stress (Landers et al., 2025).

MICROBIOME-CONSCIOUS ORAL HYGIENE

An emerging concept in oral-systemic medicine is that oral health should focus on preservation of a balanced microbial ecosystem rather than indiscriminate elimination of bacteria. While antiseptic mouthrinses have important short-term clinical applications, prolonged routine use may disrupt beneficial oral microbial communities involved in nitrate metabolism and vascular regulation (Bondonno et al., 2015; Landers et al., 2025; Tribble et al., 2019).

Studies have shown that antibacterial mouthwashes can impair enterosalivary nitrate reduction and may adversely affect blood pressure regulation through suppression of nitrate-reducing commensal bacteria (Bondonno et al., 2015; Tribble et al., 2019). Although these findings are not specific to AD, they are relevant to the vascular component of the oral–brain axis. Consequently, routine oral hygiene should emphasize effective mechanical plaque control while reserving broad-spectrum antiseptic therapies for specific clinical indications.

TONGUE CLEANING

The tongue dorsum serves as a major microbial reservoir within the oral cavity and contributes substantially to oral microbial ecology. Regular tongue cleaning has been associated with reductions in tongue coating, oral malodor, and local inflammatory burden while supporting populations of nitrate-reducing bacteria involved in nitric oxide metabolism (Tribble et al., 2019).

From a neurologic perspective, the potential benefits of tongue cleaning are likely indirect and mediated primarily through improvements in oral microbial balance and vascular physiology rather than disease-specific effects. Nonetheless, tongue cleaning represents a simple, low-cost intervention that complements broader oral-health practices and may support maintenance of a healthier oral microbiome (Landers et al., 2025).

EMERGING MICROBIOME-BASED INTERVENTIONS

Growing interest has focused on probiotic and postbiotic approaches designed to promote oral microbial

homeostasis. Clinical studies have reported improvements in gingival inflammation and plaque accumulation with specific strains such as Streptococcus salivarius M18 and heat-treated Lactobacillus plantarum L-137 (Babina et al., 2023; Iwasaki et al., 2016). Although these findings are encouraging, evidence remains insufficient to recommend such interventions as primary therapies.

At present, microbiome-based approaches should be considered adjunctive strategies that complement, rather than replace, conventional periodontal treatment and mechanical plaque control. Their potential relevance to AD prevention remains speculative and requires further investigation.

SALIVARY DIAGNOSTICS AND DIGITAL RISK ASSESSMENT

One of the most promising translational developments is the emergence of salivary diagnostics and digital periodontal assessment technologies. Saliva contains inflammatory mediators, microbial biomarkers, and host-response molecules that may provide insight into periodontal disease activity and systemic health status (Landers et al., 2025). Similarly, artificial intelligence-assisted periodontal imaging and digital risk-stratification tools may facilitate earlier identification of individuals with clinically significant periodontal disease (Wu & Tsoi, 2025).

Although these technologies are not currently validated as dementia-screening tools, they may prove valuable in future interdisciplinary studies investigating the relationship between oral health and neurodegenerative disease. Earlier detection and management of periodontal inflammation could become an important component of precision prevention strategies that integrate oral, vascular, metabolic, and neurologic risk assessment.

TRANSLATIONAL PERSPECTIVE

The strongest clinical message emerging from the oral–brain literature is not that oral-health interventions have been proven to prevent Alzheimer's disease. Rather, it is that periodontal disease represents a plausible and potentially modifiable contributor to systemic inflammatory and vascular burden. Given the safety, accessibility, and established oral-health benefits of periodontal prevention and treatment, these interventions can be recommended confidently as part of comprehensive health promotion while the field continues to investigate their effects on long-term neurologic outcomes (Landers et al., 2025).

This perspective is consistent with contemporary approaches to AD prevention, which increasingly emphasize management of modifiable risk factors across the lifespan. Within that framework, maintenance of periodontal health should be viewed not as a substitute for established neurologic risk-reduction strategies, but as a complementary component of a broader precision-prevention model for healthy aging.

CLINICAL IMPLICATIONS

The principal clinical implication of the oral–brain axis is not that periodontitis should be viewed as a proven cause of Alzheimer's disease, but rather that it represents a plausible and potentially modifiable contributor to neurodegenerative risk biology (Hajishengallis & Chavakis, 2021; Landers et al., 2025). The convergence of epidemiologic, neuropathologic, and mechanistic evidence suggests that chronic periodontal inflammation may influence several pathways relevant to AD, including systemic inflammation, vascular dysfunction, blood-brain barrier integrity, innate immune activation, and proteinopathy (Dominy et al., 2019; Hajishengallis & Chavakis, 2021; Ising et al., 2019; Landers et al., 2025; Montagne et al., 2020; Poole et al., 2013; Sanz et al., 2020; Sweeney et al., 2018).

This perspective supports greater integration of oral health into discussions of healthy cognitive aging. Patients with mild cognitive impairment, significant vascular risk factors, or a family history of dementia may benefit from routine assessment of oral health status as part of comprehensive preventive care. Likewise, clinicians should recognize that poor oral health may be associated with cognitive decline and may also arise as a consequence of it, creating a cycle in which worsening cognition impairs oral hygiene while chronic oral inflammation may further amplify systemic disease burden.

The most practical recommendation at present is interdisciplinary collaboration. Neurologists, primary care physicians, geriatricians, and dental professionals frequently manage overlapping patient populations yet often do so independently. Improved communication and referral pathways may facilitate earlier identification and treatment of periodontal disease while reinforcing broader preventive strategies aimed at preserving vascular, metabolic, and neurologic health (Landers et al., 2025).

Importantly, periodontal therapy should not be promoted as a proven dementia-prevention intervention. Rather, maintenance of periodontal health should be viewed as a low-risk, evidence-based component of comprehensive health promotion that aligns with contemporary approaches to risk reduction in aging populations.

GINGIPAIN INHIBITORS

Among the proposed links between periodontitis and Alzheimer's disease, gingipains provide one of the clearest pharmacologic test cases of the oral–brain axis. These Porphyromonas gingivalis cysteine proteases comprise arginine-specific enzymes (RgpA and RgpB) and a lysine-specific enzyme (Kgp), which contribute to host-protein degradation, immune evasion, and tissue injury. Their inhibition is therefore mechanistically attractive because it could reduce a defined virulence pathway without assuming that periodontal dysbiosis acts through a single inflammatory mediator (Li & Collyer, 2011; Sheets et al., 2005).

Preclinical studies support this rationale but do not establish clinical translatability. In experimental systems, gingipain inhibition reduced indices of bacterial virulence and tissue injury, and Kgp-directed small molecules were reported to lessen P. gingivalis–associated neuropathologic changes in murine models (Dominy et al., 2019). Separate periodontal studies have demonstrated benefit with dual Rgp/Kgp inhibition, underscoring that the preclinical literature encompasses more than one inhibitor strategy (Kataoka et al., 2014). A recent systematic review likewise identified generally favorable findings across periodontal and associated systemic-disease models, although the

evidence was predominantly preclinical and heterogeneous (Pedrosa et al., 2025).

Clinical translation, however, remains unproven. Atuzaginstat (COR388), an oral Kgp inhibitor, provided the first large clinical test of this hypothesis in patients with mild-to-moderate Alzheimer's disease (Sabbagh & Decourt, 2022). The phase 2/3 GAIN trial did not meet its co-primary cognitive and functional endpoints, and treatment was associated with liver-enzyme abnormalities that complicated chronic administration (Sabbagh & Decourt, 2022; Sabbagh, 2023). Although exploratory subgroup and biomarker analyses have been reported, these findings were post hoc and should be regarded as hypothesis-generating rather than evidence of efficacy (Sabbagh, 2023).

Taken together, these findings argue more for caution than abandonment. The negative GAIN experience does not eliminate gingipains as biologically relevant virulence factors, but it indicates that targeting this pathway alone has not produced validated disease modification in symptomatic Alzheimer's disease. Within the broader oral–brain framework advanced in this review, gingipain inhibition therefore remains biologically plausible but clinically unvalidated. Future development will require safer compounds, validated measures of target engagement, earlier intervention, and more precise selection of patients in whom P. gingivalis–associated pathology is demonstrably active (Pedrosa et al., 2025; Sabbagh & Decourt, 2022; Sabbagh, 2023).

FUTURE DIRECTIONS

Future research must move beyond associative epidemiology toward mechanistically informed human studies capable of determining whether periodontal disease influences the trajectory of Alzheimer's disease. The most important unanswered question is not whether periodontal disease and AD are associated, but whether treatment of periodontal inflammation alters validated markers of neurodegenerative risk or progression.

Prospective clinical trials should evaluate the effects of intensive periodontal therapy on AD-relevant outcomes, including plasma and cerebrospinal fluid biomarkers, amyloid and tau imaging, blood-brain barrier integrity, cerebrovascular function, neurofilament light concentrations, and longitudinal cognitive performance. Such studies should also account for important modifiers including APOE genotype, diabetes mellitus, smoking status, cardiovascular disease, and socioeconomic factors, all of which may influence susceptibility to both periodontal disease and neurodegeneration (Bell et al., 2012; Liu et al., 2013; Montagne et al., 2020; Sanz et al., 2020).

Additional work is needed to clarify the relative contributions of specific mechanisms discussed in this review, particularly gingipain biology, extracellular vesicle signaling, oral–gut–brain interactions, and vascular dysfunction. Integration of salivary diagnostics, digital periodontal phenotyping, and multi-omics approaches may further improve understanding of how oral health interacts with systemic and neurologic disease processes.

Ultimately, the field must determine whether periodontitis functions primarily as a risk marker of systemic vulnerability, a potential contributor to AD-related biology, or a true disease accelerator. Resolving this question will require close collaboration among neuroscientists, dentists, immunologists, vascular biologists, and epidemiologists.

CONCLUSION

Periodontitis is associated with Alzheimer's disease and may be a potential contributor through interconnected inflammatory, microbial, vascular, neuroimmune, and neurodegenerative pathways. Current evidence supports biologic plausibility and association but does not establish periodontitis as a causal or modifiable AD risk factor. Periodontal health should be maintained for established oral and general-health benefits. Whether periodontal prevention or treatment alters AD incidence, biomarker progression, or cognitive decline remains unproven and requires prospective interventional study.

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The authors declare no conflicts of interest.

INFORMED CONSENT

Not applicable. This manuscript is a narrative review and does not report new human-participant data.

AUTHOR CONTRIBUTIONS

Josh Landers: conceptualization, literature review, drafting, revision, visualization, and supervision; Alexis Clement: conceptualization, drafting, visualization, and supervision; Forest Kelly: conceptualization, drafting, and revision.

DATA AVAILABILITY

Not applicable. No new data were created or analyzed in this narrative review

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