Infection and Drug Resistance

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Association Between *Porphyromonas gingivalis* and Alzheimer's Disease: A Comprehensive Review

Jéssica María Sarmiento-Ordóñez[1,2], Dayvid Rafael Brito-Samaniego[3], Ana Cristina Vásquez-Palacios[1], Edisson-Mauricio Pacheco-Quito[1,2]

[1]Unidad Académica de Salud y Bienestar, Facultad de Odontología, Universidad Católica de Cuenca, Cuenca, Ecuador; [2]Grupo de Investigación Innovación y Desarrollo Farmacéutico en Odontología, Facultad de Odontología, Jefatura de Investigación e Innovación, Universidad Católica de Cuenca, Cuenca, Ecuador; [3]Ministry of Public Health of Ecuador, Dentistry Department, Cuenca, Ecuador

Correspondence: Edisson-Mauricio Pacheco-Quito, Unidad Académica de Salud y Bienestar, Facultad de Odontología, Universidad Católica de Cuenca, Cuenca, Ecuador, Email epachecoq@ucacue.edu.ec

Background: Periodontitis has long been linked to various inflammatory, chronic, and immunological diseases, such as heart disease or diabetes. Recently, there has been increasing scientific interest in the bidirectional relationship that may exist between periodontitis and the presence and progression of Alzheimer's disease (AD), where it is hypothesized that the infiltration of oral microorganisms (mainly *Porphyromonas gingivalis*) into the bloodstream, which subsequently reaches the brain, causes inflammatory and neurodegenerative processes related to AD.

Purpose: The purpose of this review is to determine the association between *Porphyromonas gingivalis* and Alzheimer's disease in older adults.

Patients and Methods: It was carried out using different databases such as PubMed, Web of Science, among others, of no more than 10 years old focused on older adult patients who have presented periodontitis and Alzheimer's disease. MESH-indexed terms were used, getting 307 articles. After removing 206 duplicates and applying inclusion criteria (language, relevance, and contribution to the study's objectives), 24 articles were selected for analysis.

Conclusion: Evidence has been found that gingipains produced by *P. gingivalis* may contribute to the formation of amyloid plaques in the brain and nerve cell damage characteristic of Alzheimer's disease. It has also been observed that *P. gingivalis* can enter the brain and stimulate a local immune response. Although the association is promising, more research is needed to confirm it and to develop effective treatments. These findings may have significant implications for clinical practice, potentially leading to preventive or therapeutic strategies targeting oral health as a modifiable risk factor for AD. Further research could focus on exploring these pathways and developing targeted interventions.

Keywords: periodontitis, Alzheimer's disease, *Porphyromonas gingivalis*, older adults

Introduction

According to the Global Burden of Disease Study (2016), periodontitis had been ranked as the 11th most prevalent condition worldwide. Its prevalence varies between 20% and 50% globally. This disease significantly contributes to tooth loss, thereby impacting essential functions such as chewing, aesthetics, confidence, and overall quality of life. In 2016, periodontitis accounted for 3.5 million years lived with disability on a global scale.[1] In the United States, periodontitis affects over 40–46% of adults aged 30 and above.[2,3] Zini et al mentions that over 10% contend with severe manifestations of the condition. Moreover, prevalence escalates notably, affecting between 70% and 85% of individuals in the 60 to 65 ages.[4,5]

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting structures. It involves the formation of periodontal pockets, clinical attachment loss, and alveolar bone resorption, which can ultimately lead to tooth loss. According to the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, periodontitis results from

Received: 22 October 2024
Accepted: 13 March 2025
Published: 25 April 2025

a complex interplay between microbial dysbiosis and a dysregulated host immune-inflammatory response. While gingivitis, an inflammation confined to the gingival tissues, is a common precursor, it does not always progress to periodontitis, as additional genetic, environmental, and systemic factors influence disease susceptibility and progression.[6–8] Periodontitis is associated with a shift in the subgingival microbial community, with an increased presence of keystone pathogens such as *Porphyromonas gingivalis, Tannerella forsythia*, and *Treponema denticola* collectively known as the red complex contributing to a dysbiotic pathobiome.[9–12] This chronic condition, which has a high global prevalence, has also been linked to various systemic diseases, including cardiovascular diseases, diabetes mellitus, certain types of cancer, and neurodegenerative disorders such as Alzheimer's disease.[13–15]

Alzheimer's disease is a form of dementia characterized by a progressive deterioration of memory, thinking, language, and learning ability.[16–19] It is the most common type of dementia and affects more than 37 million people worldwide, especially people over 65 years of age.[20–22] It is estimated that one in 85 people will have this disease by 2050 due to increased life expectancy and lifestyle changes.[23–25]

Pathogenesis starts in the neuron; interneuronal connections depend on the correct functioning of the neurons. Two structural proteins highly influence interneuronal functioning, the β-amyloid protein and the Tau protein.[26–28] The β-amyloid precursor protein (β-APP) is a membrane glycoprotein and a usual component of neuron membranes, its function is mainly related to cell adhesion processes, neuronal cell repair, and growth; at this point, intraneuronal β- and γ-secretase enzymes play an important role in the processing of β-APP. The β-secretase cleaves or cleaves β-APP, creating a fragment called C99. Then, γ-secretase processes C99 and produces amyloid beta (Aβ) peptides; these fragments are insoluble and bind to each other forming a glycopeptide in the extracellular space; which start to assemble and constitute amyloid plaques, which accumulate and block the reception of neurotransmitters interfering with synapses of neurons and triggers the inflammatory response, which also influences AD symptoms.[26,28,29]

This first process is followed by the intervention of another intracellular structural protein, the Tau protein, which is part of the microtubules, which in turn form the cytoskeleton of the cell. The function of microtubules is not only to stabilize the cell but also to serve as rails or bridges for the transport of molecules or proteins through them. Understanding this, the formation of amyloid plaques activates protein kinases, enzymes that will phosphorylate the Tau protein, ie to place a phosphate group in its structure, which results in the separation of the microtubules, triggering their structural decomposition; without these, the passage of molecules from one end of the cell to the other cannot occur. Furthermore, all phosphorylated Tau proteins begin to form a network of agglomerations known as Tau tangles, fibrillar and insoluble in the cytoplasm of the cell.[26,28] When these two processes occur, in which neurotransmitters cannot be transported through the cell employing the microtubules and neuronal synapsis cannot take place due to the formation of amyloid plaques, the neuron stops functioning properly, which leads to apoptosis (Figure 1).[26]

Hypotheses of the Origin of Alzheimer's Disease

Symptoms of Alzheimer's disease may begin decades before the clinical onset of symptoms and are thought to be caused by the formation of beta-amyloid plaques, neuroinflammation, and Tau protein tangles.[14,23–26,30–33] Therefore, two main hypotheses have emerged in the current literature regarding the development of Alzheimer's disease:

- Amyloid cascade hypothesis: suggests that AD is caused by excessive production of a protein called amyloid beta (Aβ) through a process known as primary amyloidosis. This theory also suggests that toxic Aβ fibrils accumulate in the brain and promote neurodegeneration.[24,25,30,34]
- Mitochondrial cascade hypothesis: proposes that AD is related to brain aging and mitochondrial dysfunction, leading to excessive production of reactive oxygen species (ROS) resulting in a vicious cycle of mitochondrial dysfunction. This hypothesis also suggests that this mitochondrial dysfunction may promote programmed cell death and excessive Aβ formation, which in turn triggers an inflammatory response in the brain that can damage nerve cells and reduce levels of certain neurotransmitters important for memory and other brain functions.[30,35–37]

In both cases, the accumulation of beta-amyloid plaques in the brain can have direct and indirect toxic effects on neurons and the connections between them, as well as the blood-brain barrier. In addition, phosphorylation and cleavage of tau

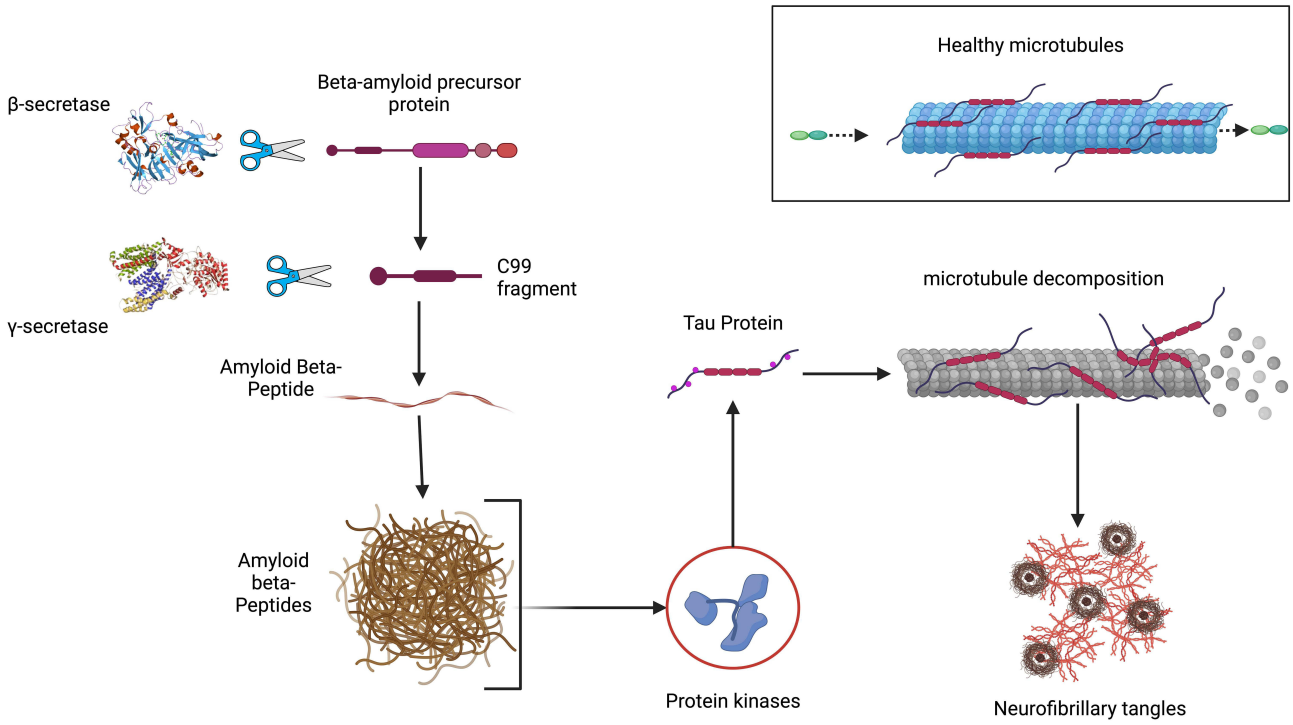

Figure 1 Representation of the pathophysiology of Alzheimer's disease.
Note: Author's own work. Created in BioRender. Brito, D. (2025) https://BioRender.com/k75f257.

proteins can lead to the formation of toxic neurofibrillary tangles that contribute to neuronal damage and loss of memory and other cognitive functions.[14,23,26,30–33,35,38–40]

Microbiological Characteristics of *P. gingivalis*

Periodontitis is described as chronic inflammation caused by the presence of gram-negative bacteria in the host, which cause connective tissue breakdown, formation of periodontal pockets, decreased alveolar bone structure, bleeding on probing, and a swollen and discolored appearance of the gingiva.[41,42] This situation becomes more chaotic as the patient ages if we add many years of bad oral habits, such as smoking, alcohol consumption, and poor oral hygiene.[26,43–46] Periodontitis has long been linked to various inflammatory, chronic, and immunological diseases, such as heart disease or diabetes; however, scientific interest in the bidirectional relationship between periodontitis and the presence and progression of Alzheimer's disease (AD) has recently increased because several studies show that aspects, such as gingival inflammation, periodontal pockets, loss of clinical attachment level, were much more prevalent in patients with dementia.[13,16,20,26,31,46] It is also hypothesized that the infiltration of oral microorganisms (mainly *P. gingivalis*) into the bloodstream, which subsequently reaches the central nervous system (CNS), causes inflammatory processes related to AD.[42]

P. gingivalis is the most characteristic pathogen in periodontitis as it modulates the size and composition of the local microbial community to promote periodontitis and an inflammatory milieu with the help of secretion of gingipains, theses are proteolytic enzymes with the ability to break down proteins in the body, including those found in the brain as it can escape into the bloodstream and colonize extraoral tissues (Figure 2). Inhibition of gingipains may prevent *P. gingivalis* from thriving and/or proliferating. The inhibition of gingipains cannot be done naturally but can be achieved through chemical inhibitors that block their enzymatic activity, natural compounds derived from plants or microorganisms, vaccines that stimulate a specific immune response against these enzymes, and nanotechnology that delivers inhibitors directly to the bacterial environment. These strategies aim to prevent gingipains from degrading host proteins, thereby stopping *P. gingivalis* from thriving and causing periodontal diseases.[47–49]

https://doi.org/10.2147/IDR.S491628

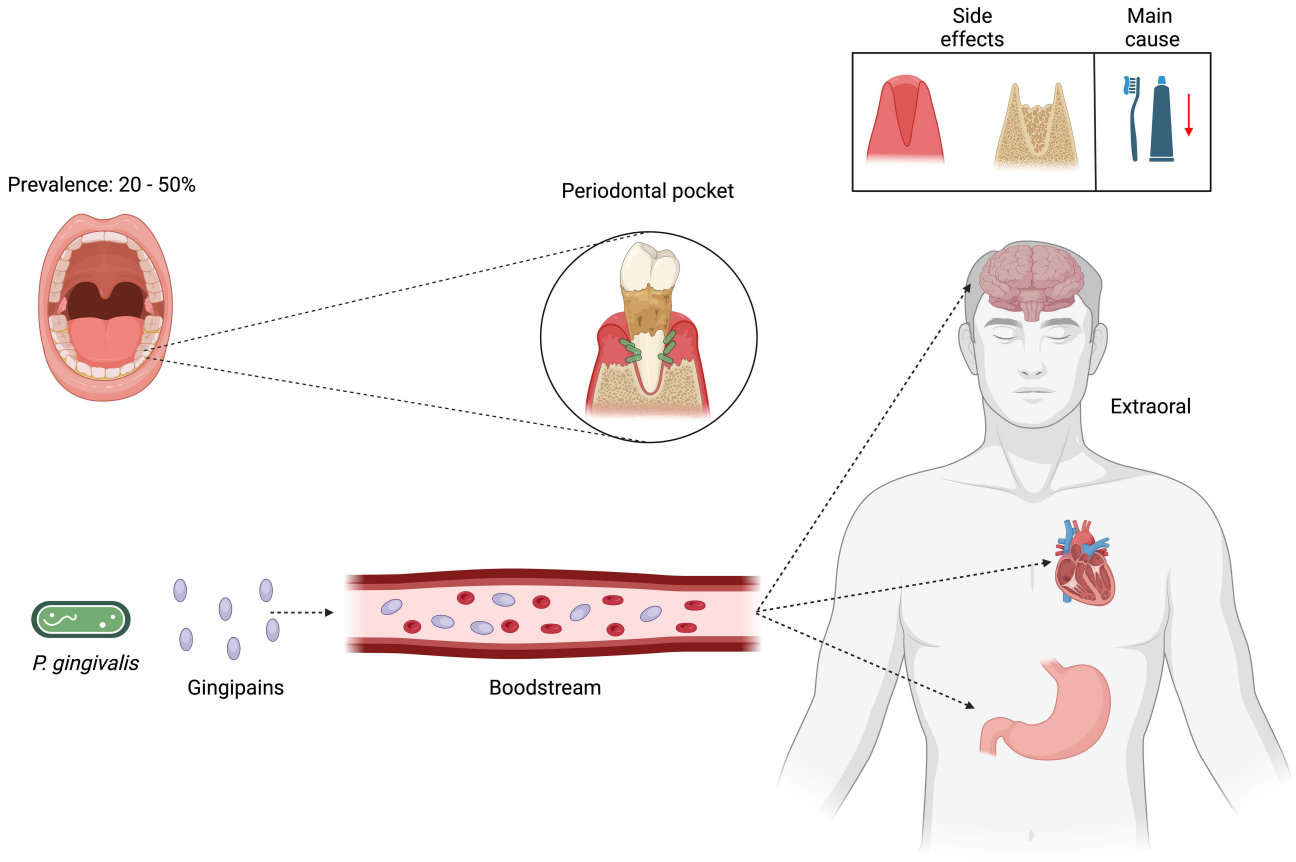

Figure 2 Representation of the way in which *P. gingivalis* and its toxins can migrate extra orally.
Note: Author's own work. Created in BioRender. Brito, D. (2025) https://BioRender.com/f60d407.

In recent years, there has been increasing interest in the role that this bacterium may play in the onset and development of Alzheimer's disease.[30,50–53] Several studies have found evidence suggesting the validity of this hypothesis; for example, one study found that patients with Alzheimer's disease had higher levels of antibodies to *P. gingivalis* in their cerebrospinal fluid than the control group.[54–56] Another study found that people with periodontitis were more likely to develop dementia and Alzheimer's disease.[47–49] It is believed that *P. gingivalis* can enter the CNS through the blood-brain barrier (BBB). Under certain conditions, such as chronic inflammation, the BBB can become more permeable and allow the passage of substances that should not normally pass through it.[55,57–59] Two pathways have been considered by which *P. gingivalis* can cross the BBB; it can be by transcytosis known as the "transcellular pathway" or by loss of the intercellular junction of the microvascular endothelial cells of the brain (BMECs) known as the "extracellular pathway", which are part of the blood-brain barrier structure.[60]

Gingipains, LPS and outer membrane vesicles produced by *P. gingivalis* can degrade proteins in the extracellular matrix and BMECs including tau protein (found in the neurofibrillary tangles characteristic of Alzheimer's disease), which can weaken its integrity, allowing the bacteria to pass into the brain (extracellular pathway). Once *P. gingivalis* enters the brain, it can cause neuronal damage and contribute to neuroinflammation and amyloid plaque formation, which has been linked to the pathogenesis of Alzheimer's disease.[47–49,60,61] Following the transcellular pathway there is an increase in transcytosis due to the ability of *P. gingivalis* to bind specifically to caveolin-1 which is a protein of caveolae, structures that are part of the invagination of the cell membrane that are directly related to the process of transcytosis.[60]

Although further studies are still needed to confirm the exact role of *P. gingivalis* and its gingipains in the pathogenesis of Alzheimer's disease, current findings suggest that these bacteria and their enzymes may play an important role in its development. Therefore, maintaining good oral hygiene and preventing or treating periodontitis may be important in reducing the risk of developing neurodegenerative diseases.[43,48,49]

Gingipains

Gingipains are specialized enzymes that play a crucial role in the pathogenesis of periodontitis and can have detrimental effects on the host, being directly involved in periodontal tissue damage. They are known for their ability to degrade proteins such as collagen, which is key in connective tissues. The resorption of the crest of bone, rather than just collagen degradation, is necessary for the formation of periodontal pockets. This resorption facilitates the colonization and proliferation of periodontopathogenic bacteria in these areas. In turn, these enzymes can interfere with the function of immune cells, such as leukocytes, and modulate the inflammatory response in periodontal tissue, contributing to the chronicity of periodontitis and promoting ongoing destruction.[62,63]

Gingipains are classified into three main types: arginine-specific gingipain A (RgpA), arginine-specific gingipain B (RgpB) and lysine-specific gingipain (Kgp).

i. RgpA and RgpB are proteases that contribute to the deterioration of periodontal tissue by degrading essential proteins such as collagen. These enzymes can break down the structural components of connective tissue, which weakens tooth support and promotes bone loss. In addition, it has been observed that gingipains RgpA and RgpB also play a role in evading the host immune response. These enzymes may alter the activity of immune cells, inhibiting their ability to fight bacterial infection and thus favoring the persistence of *P. gingivalis* in the oral cavity.[63,64]
ii. Kgp, a lysine-specific protease, also plays an important role in the virulence of *P. gingivalis*. Kgp acts as a factor that facilitates the co-aggregation of *P. gingivalis* with other oral bacteria, leading to the formation and stability of dental biofilm and making it difficult to remove by conventional oral hygiene techniques, such as brushing and flossing.[65,66] These biofilms are highly organized microbial communities attached to the tooth surface, which play a key role in the progression of periodontitis.[64,66,67]

These enzymes can spread through the bloodstream and affect other organs, such as the heart and brain. Gingipains may contribute to this association by inducing chronic and systemic inflammation, activating blood clotting, and promoting the formation of atherosclerotic plaques.[66,68]

Relationship Between Periodontitis and Alzheimer's Disease

Periodontitis is associated with Alzheimer's disease (AD) through three main mechanisms: direct invasion of periodontopathogens, increased inflammatory markers, and atherosclerotic plaque formation. First, periodontopathogens may enter the systemic circulation and cross the blood-brain barrier to invade the brain, which may stimulate cytokine production and increase the inflammatory state.[69–71] Second, periodontitis may contribute to the development of dementia by inducing a systemic inflammatory state and releasing proinflammatory cytokines.[69,70,72,73] Finally, periodontitis may cause damage to endothelial cells due to toxins released by the bacteria involved, leading to an increase in atherosclerotic plaques and an increased risk of dementia due to loss of blood flow, which reduces the supply of oxygen and nutrients to the brain.[6,20,24,25]

In the last decade, an increasing number of clinical reports have linked periodontitis to the development of dementia, and the putative mechanisms include pathogen entry through the trigeminal nerve, pathogen invasion into the bloodstream through neovascularization at the blood-brain barrier, and microorganism-induced amyloidogenesis. A more recent study using an animal model of periodontitis and human postmortem brain tissue from subjects with Alzheimer's disease indicates that *P. gingivalis* and/or its product, gingipain, translocate to the brain.[50,74,75] Furthermore, in another study provides evidence that *P. gingivalis* and its bacterial by-products may result in repeated exposure of distant organs such as the brain, liver, and pancreas to bacteria and their by-products.[76–78] Periodontal pathogens and the host immunoinflammatory response in periodontitis can affect brain function, especially in more vulnerable elderly subjects, and may contribute to the onset and progression of neurodegenerative disorders.[51,58]

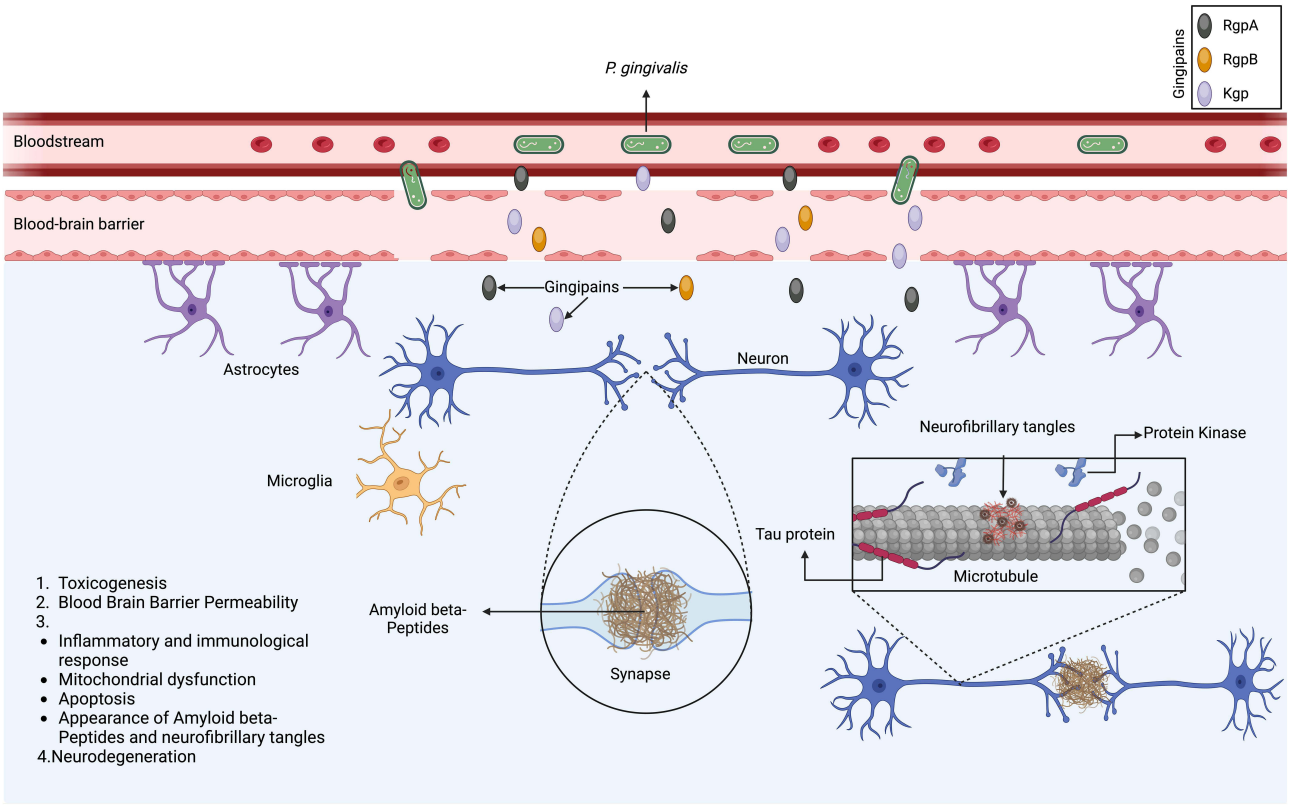

Figure 3 Process by which *P. gingivalis* and gingipains can induce the appearance and development of Alzheimer's disease.
Note: Author's own work. Created in BioRender. Brito, D. (2025) https://BioRender.com/t16q296.

Some putative mechanisms that could explain how periodontitis may affect CNS homeostasis have been described by experimental studies and include (i) translocation of bacteria into the bloodstream (bacteremia) or invasion into the brain via the trigeminal nerve (eg, *Porphyromonas gingivalis*) and (ii) production of proinflammatory cytokines that enter the bloodstream and act systemically or reach the brain via the peripheral nerve pathway (Figure 3). [59,79–82]

The current evidence linking *P. gingivalis* to Alzheimer's disease, while compelling, is subject to significant limitations that warrant cautious interpretation. A major constraint is the reliance on animal models and in vitro studies, which, while valuable, may not fully replicate the complexity of human physiology and pathology.[83] Furthermore, many studies fail to account for potential confounding factors, such as genetic predispositions, lifestyle influences, or comorbidities, which could also contribute to neuroinflammation and cognitive decline. Additionally, the exact mechanisms by which *P. gingivalis* might induce neuroinflammation, whether through systemic circulation, direct neural pathways, or other routes, remain inadequately explored. Another notable limitation is the narrow focus on select pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, without encompassing the broader spectrum of inflammatory mediators that may be involved in the disease process. These gaps highlight the need for more comprehensive, longitudinal human studies to validate these findings and better elucidate the intricate relationship between periodontal infections and Alzheimer's disease.[54,83–86]

Bidirectionality

A bidirectional relationship between periodontitis and Alzheimer's disease (AD) has been suggested, with evidence pointing to overlapping biological and behavioral factors. On the one hand, AD can contribute to poor oral hygiene due to cognitive decline, reduced manual dexterity, or difficulty accessing dental care, all of which increase the risk of periodontal infection and tooth loss. Studies indicate that individuals with dementia are more likely to require assistance with toothbrushing, and their inability to perform effective plaque control may exacerbate oral health issues. However,

poor hygiene alone is insufficient to cause periodontitis; factors such as immune dysfunction, genetic predisposition, and the presence of pathogenic bacteria are also critical in its development.[43,54,87]

On the other hand, periodontitis itself may play a role in exacerbating AD. For example, elevated levels of pro-inflammatory cytokines, originating from periodontal tissue, have been associated with cognitive decline and amyloid plaque deposition, hallmark features of AD. Additionally, some studies suggest that periodontal pathogens like *P. gingivalis* may invade the brain through hematogenous routes or cranial nerves, potentially contributing to neuroinflammation and neuronal damage.

This complex interplay highlights the possibility that AD and periodontitis not only share risk factors but also influence each other through behavioral, inflammatory, and microbiological pathways, emphasizing the importance of managing both conditions holistically.[15,30]

Experiments in vivo

Dominy et al developed an experiment in mice to investigate the relationship between oral infection with *P. gingivalis* and the development of AD. To carry out the experiment, mice were infected with this bacterium for 6 weeks. Then, the mice were sacrificed to collect their brains and analyze them.[88] To analyze the effects on the brains of the mice, several techniques were used. Histological tests were performed to examine amyloid plaques and neurofibrillary fibrils in the brain. Biochemical tests were also performed to measure the levels of A-beta-42 and Tau in the brain, which are widely used indicators to determine whether dementia is related to AD. Finally, molecular techniques to analyze the presence of *P. gingivalis* and its toxic products in the brain. The results of the study showed that oral infection with *P. gingivalis* in mice resulted in colonization of the brain and increased production of A-beta-42, a component of amyloid plaques found in the brains of patients with Alzheimer's disease.[11,88,89] In addition, gingipains produced by the bacteria were shown to be neurotoxic both in vivo and in vitro and exerted detrimental effects on Tau protein, a protein necessary for normal neuronal function.[12,31,88,89] The researchers also tested a specific inhibitor (compound or drug that can stop or reduce activity) in mice and found that it significantly reduced the bacterial load in the brain and improved cognitive function. This suggests that small-molecule inhibitors may be effective in treating Alzheimer's disease by inhibiting gingipain production.[26,56,88]

In another study, Lu et al analyzed the effect of continuous administration of salivary microbiota in APPswe/PS1ΔE9 (PAP) transgenic mice (genetically modified mice infected with amyloid-reducing protein to develop features related to Alzheimer's disease) for two months. The mice were divided into two groups: one received salivary microbiota from patients with periodontitis (group P) and the other received salivary microbiota from healthy individuals (group H). Then, an object was presented to the PAP transgenic mice after they had been familiarized with two identical objects previously. The time the mice spent exploring the novel object was used as a measure of their long-term cognitive ability. The results showed that the P group presented a significant decrease in novel object exploration, indicating a decrease in long-term cognitive ability. Furthermore, impairments in learning and short-term memory were observed in the P group compared to the H group. Mice in the P group were also found to have increased levels of beta-amyloid and neuroinflammation. The results suggest that periodontitis-related salivary microbiota may aggravate cognitive impairments and increase beta-amyloid accumulation and neuroinflammation in PAP transgenic mice.[90]

Ilievski et al conducted a study to investigate the impact of chronic oral application of a periodontal pathogen on brain health in wild type mice. The researchers induced periodontitis in 8-week-old C57BL/6 wild type mice by repeatedly applying *P. gingivalis* over a 22-week period. The mice were divided into experimental and control groups, with the experimental group receiving *P. gingivalis* and the control group receiving a vehicle alone. Bone loss around teeth was assessed to confirm periodontitis development, and body weight and food consumption were monitored throughout the study. After 22 weeks, the mice were sacrificed, and their brains were collected for analysis. Immunofluorescence, confocal microscopy, and immunohistochemistry techniques were used to detect markers such as Aβ42, intact neurons, microglia, astrocytes, and proinflammatory cytokines in the brain tissue. Gene expression levels of key genes associated with Alzheimer's disease pathology, including APP, BACE1, ADAM10, PSEN1, and Tau, were also analyzed.[91] The results showed significant neuroinflammation in the hippocampus of mice in the experimental group, with elevated levels of proinflammatory cytokines IL6, IL1β, and TNFα. Increased astrocyte numbers indicated astrocyte activation, while

a decrease in intact neuronal cells and an increase in degenerating neurons suggested neurodegeneration. Extracellular Aβ42 plaques were detected in the brains of experimental mice, indicating increased amyloid beta production. Pg/gingipain was found in various locations within the hippocampus of mice following oral application of *P. gingivalis*. Additionally, altered gene expression levels of APP, BACE1, ADAM10, PSEN1, and Tau were observed in the experimental group, reflecting changes associated with Alzheimer's disease pathology.[91]

Eri Ishida and collaborators from various departments at Hiroshima University utilized a gestational mouse model to investigate the impact of maternal odontogenic infection with *P. gingivalis* on offspring behavior and brain tissue. The experimental protocol involved infecting five-week-old female mice with *P. gingivalis*, initiating mating 6 weeks post-infection, conducting the passive avoidance test on the offspring at 45 days after birth and collecting brain tissue post-test. The results revealed that offspring from *P. gingivalis*-infected mothers exhibited reduced cognitive function, as evidenced by a shorter latency in the step-through passive avoidance test. *P. gingivalis* was observed to be widely distributed in the brain, particularly in the hippocampus, leading to decreased numbers of neuron cells and cyclic adenosine monophosphate response element-binding protein-positive cells in the hippocampus and amygdala. Moreover, there was an increase in ionized calcium-binding adapter protein 1-positive microglia and glial fibrillary acidic protein-positive astrocytes in the hippocampus.[92]

A study carried out by Tetsuro Morikawa et al employed several methods to analyze neprilysin expression in the hippocampus of mice. RNA was extracted from the tissues and quantitative reverse transcription was performed to measure neprilysin expression at the mRNA level. Furthermore, Western blotting assays were carried out to analyze the expression of neprilysin at the protein level in hippocampal tissues. This process included the use of a polyacrylamide gel electrophoresis and lysis kit followed by protein transfer to polyvinylidene membranes for the detection of neprilysin. Throughout the study, it was evident that systemic administration of *P. gingivalis* lipopolysaccharide (PG-LPS) caused a significant decrease in neprilysin expression in SAMP8 mice, a model of accelerated aging. It was found that both the expression of neprilysin at the mRNA level and at the protein level was significantly lower in the SAMP8 (senescence-accelerated mouse prone 8) mice treated with PG-LPS compared to the SAMP8 control group. Furthermore, it was observed that the fluorescence intensity of neprilysin in the CA3 region of the hippocampus was significantly lower in PG-LPS-treated mice compared to control mice.[93]

Chi et al carried out a study where the Morris water maze (MWM) was used to evaluate spatial learning and memory in mice. Additionally, TUNEL testing and immunofluorescence staining were performed to evaluate apoptosis and inflammation in the brain of mice.[94] In the study, *P. gingivalis* was orally administered to mice three times a week for a month to investigate its effects on the brain and intestine. The Morris water maze (MWM) was used to assess learning and spatial memory, revealing that treated mice had significantly longer escape latency and were further from the platform compared to the control group. In the platform crossing test, a significant decrease in crossing of the target area was recorded, along with a reduction in movement time and exploration in treated mice. Moreover, in the rotarod test, treated mice showed a shorter fall time, indicating impaired motor function. The results indicate that *P. gingivalis* administration induced cognitive impairment in mice, as evidenced by poor performance in tests of learning and spatial memory. Significant changes in motor activity, exploration, and brain function were also observed in treated mice. Dysbiosis of the intestinal microbiota and neuroinflammation were identified as potential underlying mechanisms of cognitive impairment induced by *P. gingivalis*. Dysfunction of the glycmatic system may also be implicated in the observed cognitive impairment. Taken together, these findings support the hypothesis that *P. gingivalis* may play a crucial role in intestinal dysbiosis, neuroinflammation, and glycmatic system dysfunction, leading to cognitive impairment.[94]

The study conducted by Zhao et al and published in the Journal of Neuroinflammation aimed to investigate the effects of nisin, a probiotic bacteriocin, in mitigating brain microbiome dysbiosis and Alzheimer's disease-like neuroinflammation triggered by periodontitis. The methods involved using a polymicrobial mouse model of periodontitis to evaluate the impact of this disease on brain microbiome dysbiosis, neuroinflammation, Alzheimer's-related changes, and the therapeutic potential of nisin. Through 16S sequencing and real-time PCR analysis, the researchers found that nisin treatment effectively mitigated changes in the brain microbiome composition, diversity, and community structure induced by periodontitis. Nisin treatment significantly reduced the levels of periodontal pathogen DNA in the brain. The study showed that nisin treatment led to a significant decrease in the mRNA expression of pro-inflammatory cytokines (IL-1β,

IL-6, TNF-α) in the brain that were elevated by periodontal infection. Additionally, nisin treatment resulted in a marked reduction in the deposition of Aβ42, total Tau, and phosphorylated Tau in the brains of infected mice, indicating a potential protective effect against Alzheimer's disease-related pathology.[84]

Experiment in vitro

Haditsch et al conducted a study based on the infection of neurons derived from inducible human pluripotent stem cells (iPSCs) with *P. gingivalis* for 24, 48, and 72 hours. The infection was characterized using transmission electron microscopy, confocal microscopy, and bacterial colony formation assays. The expression of gingipains was monitored using immunofluorescence and real-time quantitative polymerase chain reaction (RT-qPCR), and proteolytic activity was controlled using activity-based probes. Neurodegenerative endpoints were evaluated using immunofluorescence, Western blot, and Enzyme-Linked Immunosorbent Assay (ELISA). In the course of the study, it was observed that neurons survived the initial infection and exhibited time-dependent infection-induced cell death. *P. gingivalis* was found free in the cytoplasm or in lysosomes. Infected neurons showed an accumulation of autophagic vacuoles and multivesicular bodies. Tau protein was heavily degraded, and phosphorylation increased at T231. Over time, the density of presynaptic boutons decreased. It was found that *P. gingivalis* can invade and persist in mature neurons. Infected neurons exhibited signs of neuropathology like Alzheimer's disease, including the accumulation of autophagic vacuoles and multivesicular bodies, cytoskeletal alterations, an increase in the phospho-tau/tau ratio, and loss of synapses. Infection of mature neurons derived from iPSCs by *P. gingivalis* provides a novel model system to study the cellular mechanisms leading to Alzheimer's disease and to investigate the potential of new therapeutic approaches.[95]

Materials and Methods

A literature review was carried out using different databases (PubMed, Web of Science, among others), using keywords indexed in the MESH vocabulary such as "Periodontitis", "Alzheimer Disease", "Porphyromonas gingivalis", "Older adults" and the boolean operators AND, OR and NOT were used for a more specific and precise search. In this way, 307 scientific articles were found for subsequent analysis; 206 duplicate articles were eliminated. The following inclusion criteria were applied to the remaining 101 articles: articles in English, Spanish, and Portuguese; articles that are relevant and related to the topic of study, and articles that contribute to achieving the objectives of the study. Consequently, 40 articles were excluded. Finally, 15 articles were discarded after analyzing the abstract, resulting in 25 articles that met the inclusion criteria.

Results

As can be seen, there is growing and substantiated evidence suggesting an association between periodontitis and Alzheimer's disease, specifically through the presence of *P. gingivalis*. Several experimental studies in mice[84,85,91–94] have shown that proteolytic enzymes produced by this bacterium, such as gingipains Rgp and Kgp, can trigger neuroinflammation and contribute to the neuronal damage observed in Alzheimer's disease. Similarly, deoxyribonucleic acid (DNA) from *P. gingivalis* has been found in the brains of patients with Alzheimer's disease, and at the same time, an increased accumulation of amyloid plaques and neurofibrillary tangles was observed, further supporting the idea that *P. gingivalis* may have important implications in the development and progression of neurodegenerative diseases, such as Alzheimer's disease.

Thus, proper oral health care and treatment of periodontitis may play a crucial role in preventing or delaying the onset and progression of Alzheimer's disease. Elimination of *P. gingivalis* and control of periodontal infection could help reduce the gingipain load and inflammatory response in the brain, potentially slowing disease progression. However, it is important to note that further studies are needed to fully understand the underlying mechanisms of this association and to determine whether treatment of periodontitis can effectively prevent or delay the onset of Alzheimer's disease.

Tables 1 and 2 describe the studies that show the relationship between *P. gingivalis* and Alzheimer's disease.

Table 1 Results of the Relationship Between *Porphyromonas gingivalis* and Alzheimer's Disease

Title	Type of Study	Author/year	Relevant Data	Relationship Between P.g and AD	References
Periodontitis and Cognitive Decline in Alzheimer's Disease	Prospective, observational cohort study	Ide M/2016	They suggest that periodontitis in Alzheimer's disease is associated with increased severity of dementia and cognitive impairment and increased systemic proinflammatory status. In addition, there may be some cognitive benefits of periodontal treatment on Alzheimer's patients	Gingipains can cross the blood-brain barrier and accumulate in the brain.	[38]
Periodontitis as a Modifiable Risk Factor for Dementia: A Nationwide Population-Based Cohort Study	Cohort Study	Lee et al (2017)	Periodontitis was identified as a modifiable risk factor for dementia in a nationwide cohort study, with individuals affected by periodontitis showing a significantly higher risk of developing dementia	It was observed that levels of antibodies produced in response to periodontitis increased years before the onset of cognitive impairment, suggesting that periodontitis could contribute to the risk of dementia onset.	[85]
Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched cohort study	Retrospective matched-cohort study	Chen et al (2017)	The study found that patients newly diagnosed with periodontitis between 1997 and 2004 had a significantly increased risk of developing AD compared to those without periodontitis. Cox proportional hazards regression analyses revealed that patients with periodontitis were at a higher subsequent risk of AD.	A significant difference in the cumulative risk of AD between periodontitis exposed and unexposed groups was observed after 10 years of periodontitis exposure.	[86]
The *Porphyromonas gingivalis*/ Host Interactome Shows Enrichment in GWASdb Genes Related to Alzheimer's Disease, Diabetes and Cardiovascular Diseases	Bioinformatics study	Carter et al (2017)	Host genes involved in the life cycle of *Porphyromonas gingivalis* and those responding to the pathogen-host interaction are enriched in genes associated with AD	The *P. gingivalis* interactome showed a high enrichment in GWASdb genes related to neurological disorders (cognitive disorder, dementia, and AD)	[96]
Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice	Experimental study in animals	Ilievski et al (2018)	Neuroinflammation, neurodegeneration, increased amyloid beta production, astrocyte activation, and changes in gene expression are associated with Alzheimer's disease pathology.	Studies found neuroinflammation, higher number of astrocytes in the hippocampus and increased amyloid beta production in the brains of wild type mice.	[91]
Porphyromonas gingivalis, a periodontitis causing bacterium, induces memory impairment and age-dependent neuroinflammation in mice	Experimental study in animals	Ding et al (2018)	Middle-aged mice infected with *Porphyromonas gingivalis* showed impaired learning and memory abilities. The expression levels of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β were increased in the brain tissues of middle-aged mice infected with *P. gingivalis*.	The study found that *P. gingivalis* infection had detrimental effects on cognition and led to elevated levels of pro-inflammatory cytokines specifically in middle-aged mice, impairing spatial learning and memory abilities, suggesting an age-related relationship.	[83]
Association between periodontitis and risk of Alzheimer′s disease, mild cognitive impairment and subjective cognitive decline: A case-control study.	Case- control study	Holmer J/2018	The authors note a significant association between periodontitis and an increased risk of Alzheimer's disease and mild cognitive impairment.	Previous studies suggest a possible association between *Porphyromonas gingivalis*, gingipains and Alzheimer's disease.	[87]

(*Continued*)

Table 1 (Continued).

Title	Type of Study	Author/year	Relevant Data	Relationship Between P.g and AD	References
Periodontal Pathogens and Associated Intrathecal Antibodies in Early Stages of Alzheimer's Disease	Scientific research with multivariate regression analysis and general linear models	Laugisch O/2018	He found an association between the T-tau level in the Alzheimer's disease group with both serum levels of anti-*P. gingivalis* and MCP-1/CCL-2 antibodies. In addition, it was found that periodontal pathogens can enter the brain and stimulate a local immune response. However, in patients with dementia up to the age of 70 years, periodontal pathogens do not act as triggers for the development of Alzheimer's disease.	Gingipains, which can damage brain cells and contribute to the development of Alzheimer's disease.	[97]
Association of Chronic Periodontitis on Alzheimer's Disease or Vascular Dementia	Retrospective ve cohort study	Choi S/2019	They suggest that periodontitis maybe associated with an increased risk of develop dementia.	It is mentioned that gingipain inhibitors may be useful for treating both *P. gingivalis* as the	[74]
Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors.	In vitro and in vivo study	Dominy SS/2019	It was found that oral infection with *P. gingivalis* in mice resulted in colonization of the brain and an increase in the production of Aβ1-42, a component of the amyloid plaques found in the brains of patients with Alzheimer's disease. It was also demonstrated that the gingipains produced by the bacteria were neurotoxic both in vivo and in vitro and exerted detrimental effects on T-tau.	The researchers found that *P. gingivalis* bacteria were identified in the brains of patients with Alzheimer's disease and that toxic proteases from the bacteria were also identified in the brains of Alzheimer's patients.	[88]
Alzheimer's Disease-Like Neurodegeneration in *Porphyromonas gingivalis* Infected Neurons with Persistent Expression of Active Gingipains	In vitro study	Haditsch et al (2020)	The presence of gingipains was identified in more than 90% of the postmortem brains of patients with Alzheimer's disease, with intraneuronal localization of the gingipains.	*Porphyromonas gingivalis* can persist intraneuronally in mature neurons until at least 72 hours after infection. The presence of strongly degraded tau protein with increased phosphorylation in neurons infected with *P. gingivalis* suggests a direct impact of the bacteria on tau pathology.	[95]
Helicobacter pylori, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey	National survey. Descriptive correlation	Beydoun M/2020	It is indicated that there is a significant association between periodontal pathogens and incident dementia from all causes, including Alzheimer's disease.	Provides evidence that infection of microglia with *P. gingivalis* promotes cell migration and an inflammatory response through gingipain- mediated activation of protease- activated receptor 2 in mice. In addition, it shows that chronic oral application of a periodontal the pathogen, such as *Porphyromonas gingivalis*, results in brain inflammation, neurodegeneration n and beta-amyloid production in wild-type mice.	[33]
Porphyromonas gingivalis-Induced Cognitive Impairment Is Associated With Gut Dysbiosis, Neuroinflammation, and Glymphatic Dysfunction	Experimental study in animals	Chi et al (2021)	Oral administration of *Porphyromonas gingivalis* affects cognition, intestinal microbiota, immune responses, clearance of the glycomic system, and neuroinflammation in mice.	In the Morris water maze test, mice treated with *Porphyromonas gingivalis* showed a significantly longer escape latency compared to the control group	[94]

(*Continued*)

Table 1 (Continued).

Title	Type of Study	Author/year	Relevant Data	Relationship Between P.g and AD	References
Mouse maternal odontogenic infection with *Porphyromonas gingivalis* induces cognitive decline in offspring	Experimental study in animals	Ishida et al (2023)	*P. gingivalis* was detected throughout the brain, with a notable presence in the hippocampus.	Maternal odontogenic infection with *Porphyromonas gingivalis* led to cognitive decline in the offspring, as evidenced by a significantly shorter latency in the step-through passive avoidance test.	[92]
Nisin a probiotic bacteriocin mitigates brain microbiome dysbiosis and Alzheimer's disease-like neuroinflammation triggered by periodontal disease	Experimental study in animals	Zhao et al (2023)	Nisin treatment mitigated changes in the composition, diversity, and community structure of the brain microbiome, and reduced levels of periodontal pathogen DNA in the brain induced by periodontitis.	The study demonstrated that nisin can alter the composition of the brain microbiome after periodontal infection, reduce the release of pro-inflammatory cytokines, and decrease Aβ burden and tau hyperphosphorylation, suggesting a potential role for nisin in the prevention and treatment of Alzheimer's disease	[84]
Systemic Administration of Lipopolysaccharide from *Porphyromonas gingivalis* Decreases Neprilysin Expression in the Mouse Hippocampus	Experimental study in animals	Morikawa et al (2023)	Neprilysin fluorescence intensity in the CA3 region of the hippocampus was significantly lower in PG-LPS-treated mice compared with control mice.	*P. gingivalis* can reduce neprilysin expression in elderly individuals, which could contribute to increased amyloid-β deposition in the brain.	[93]

Abbreviations: PG, *Porphyromonas gingivalis*; AD, Alzheimer Disease; GWASdb, Genome-Wide Association Study database; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; IL-1β, Interleukin-1 beta; T-tau, Total tau; MCP-1, Monocyte Chemoattractant Protein-1; CCL2, C-C motif chemokine ligand 2; Aβ1-42, beta-amyloid 1–42; DNA, deoxyribonucleic acid; Aβ, beta-amyloid; CA3, Cornu Ammonis 3; PG-LPS, Prostaglandin-Lipopolysaccharide.

Table 2 Systematic Reviews and Meta-Analyses on the Association Between *P. gingivalis* and Alzheimer's Disease

Title	Type of Study	Author/Year	Relevant Data and Statistical Results	Relationship between P.g and AD	Reference
Association Between Oral Bacteria and Alzheimer's Disease: A Systematic Review and Meta-Analysis	Systematic Review with Meta-Analysis	Liu et al (2023)	Reviewed 16 studies. Oral bacteria in the brain increased AD risk over ten-fold (OR=10.68) and six-fold for *P. gingivalis* (OR=6.84). Lower oral microbiota diversity observed in AD patients.	The presence of oral bacteria, especially *P. gingivalis*, in the brain strongly supports its involvement in AD development.	[98]
Study of *Porphyromonas gingivalis* in Periodontal Diseases: A Systematic Review and Meta-Analysis	Systematic Review with Meta-Analysis	Rafiei et al (2017)	Analyzed 49 case-control studies (5924 participants). Strong association between *P. gingivalis* and periodontal diseases (OR=9.24, p=0.000). Mean age: periodontal group 43.62 years; controls 36.56 years.	Suggests that *P. gingivalis*-driven inflammation may contribute to neurodegeneration linked to AD.	[99]
Porphyromonas gingivalis, Periodontal and Systemic Implications: A Systematic Review	Systematic Review	Fiorillo L. et al (2019)	Chronic exposure to LPS from *P. gingivalis* in mice led to β-amyloid accumulation and neurocognitive dysfunction mediated by CatB and NF-κB pathways.	Suggests a link between *P. gingivalis*-induced inflammation and Alzheimer's, with CatB as a potential therapeutic target.	[100]
Association Between Periodontitis and Cognitive Impairment in Adults: A Systematic Review	Systematic Review	Cunha P. et al (2019)	Antibodies against *P. gingivalis* correlated with cognitive decline (OR: 2.1, $p < 0.05$). Increased plasma levels of IL-6 and TNF-α were associated with severe periodontitis.	Indirect relationship supported by systemic inflammation as a key mechanism.	[101]

(*Continued*)

Table 2 (Continued).

Title	Type of Study	Author/Year	Relevant Data and Statistical Results	Relationship between P.g and AD	Reference
The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review	Systematic Review	Dioguardi M. et al (2020)	Gingipain detected in post-mortem brain tissue of AD patients. Chronic exposure to *P. gingivalis* LPS in mice caused significant cognitive deficits and β-amyloid deposition.	Supports the hypothesis of an inflammatory link between periodontitis and AD. Gingipain and β-amyloid identified as key mediators.	[47]
The Effect of Adjunctive Use of Hyaluronic Acid on Prevalence of *Porphyromonas gingivalis* in Subgingival Biofilm in Patients with Chronic Periodontitis	Systematic Review	Alshehri F. et al (2023)	No significant reductions in *P. gingivalis* prevalence observed. OR: 0.95 at 3 months and 1.11 at 6 months; p = 0.51.	Insufficient data to establish a direct link with AD.	[102]
The Role of Periodontal Bacteria, *Porphyromonas gingivalis*, in Alzheimer's Disease Pathogenesis and Aggravation: A Review	Narrative Review	Lorenzi C. et al (2021)	Studies by Poole et al detected *P. gingivalis* in brain tissue of AD patients. Increased levels of IL-1β, TNF-α, and β-amyloid were observed in animal models exposed to *P. gingivalis*.	Proposes a potential association between *P. gingivalis*-induced inflammation and AD progression.	[103]
Analysis of the Link Between Periodontal Diseases and Alzheimer's Disease	Systematic Review	Borsa L. et al (2021)	*Porphyromonas gingivalis* and Campylobacter rectus were linked to an increased incidence of Alzheimer's disease (HR = 1.22, 95% CI: 1.04–1.43, p = 0.012). Periodontitis at baseline was associated with a six-fold increase in cognitive decline over 6 months (ADAS-Cog mean change = 2.9 ± 6.6). Elevated levels of Aggregatibacter naeslundii IgG showed a higher risk for incident AD (HR = 2.0, 95% CI: 1.1–3.8).	This review highlights a significant association between periodontal pathogens and cognitive decline. Periodontitis may exacerbate Alzheimer's progression through systemic inflammation and bacterial invasion of the brain.	[32]

Abbreviations: HR, Hazard Ratio; 95% CI, Confidence Interval at 95%; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; IL-1β, Interleukin-1 beta; LPS, Lipopolysaccharides; CatB, Cathepsin B; IgG, Immunoglobulin G; OR, Odds Ratio; p, p-value.

Discussion

Several mechanisms have been proposed to associate *P. gingivalis* with neurogenerative processes. Ryder et al[26] speak of a mouth-brain translocation when gingipains promote the formation of amyloid plaques by crossing the blood-brain barrier. Lu et al[90] suggest more extensive processes, where *P. gingivalis* can move to the intestine when swallowed or aspirated, which at this point can cause changes in the intestinal microbiota generating an interaction of the gut-brain axis that can affect the blood-brain barrier, allowing the entry of bacteria and toxic products into the brain and triggering an inflammatory response and endotoxemia.[90] Additionally, Bregaint et al[104] highlight the importance of multiple experiments in mice, in which, after oral administration of *P. gingivalis*, changes in the composition of the intestinal microbiota associated with epithelial alterations and cellular barrier function have been found. Thus, despite the differences in the proposed mechanisms, it is agreed that chronic inflammation causes damage to brain cells and contributes to the accumulation of amyloid plaques and neurofibrillary tangles.[26,90,104]

According to Li et al,[105] neuroinflammation can be caused by systemic and localized inflammation at the site of periodontal infection, generated by oral dysbiosis bacteria such as *P. gingivalis*. Takeuchi et al[106] mention that the toxic products of these bacteria can induce an inflammatory response that releases proinflammatory cytokines into the bloodstream, which can reach the brain and activate resident immune cells there, such as microglia and astrocytes. These immune cells may adopt a proinflammatory phenotype and secrete their proinflammatory mediators, thus perpetuating neuroinflammation and possibly contributing to neurodegeneration.[107] Within the same premise, Bregaint et al[104] report that *P. gingivalis* can induce osteoclastogenesis and a proinflammatory response mediated by type 17 helper T cells (Th17) that is geared towards generating an inflammatory response in the organism, leading to bone damage and systemic inflammation.

Olsen I[29] mentions that gingipains are enzymes known for their ability to degrade host proteins and evade the host immune response. In the context of Alzheimer's disease, arginine-specific Gingipain A (RgpA), arginine-specific Gingipain B (RgpB), and lysine-specific Gingipain (Kgp) have been shown to have important effects on microglia residing in the brain as they can induce microglial cell migration in addition to the expression of proinflammatory cytokines. According to Xu et al,[108] Kgp. can degrade host heme proteins. Heme is an essential component of many proteins, and its degradation can interfere with normal biological processes. This can have negative effects on the host, as it alters the function of heme-dependent proteins and can affect various cellular and systemic processes. Moreover, Rgp can degrade the C5 component (protein of the complement system, which is an important part of the body's immune system) and increase inflammation. When activated in a deregulated manner, it can cause tissue damage and contribute to the pathogenesis of diseases such as periodontitis, which in turn promotes neuroinflammation by activating immune cells in the brain and increasing the production of inflammatory mediators and amyloid-beta proteins. Based on this problem, Kariu T[63] conducted research on prenylated flavonoids, which are bioactive compounds found in green tea and Epimedium species, a genus of the Berberidaceae family, where they are reported to have the ability to inhibit both gingipain-dependent virulence and bacterial growth in periodontitis sites where proteins are the only source of nutrition. It also reports that prenylation (the addition of a prenyl group to the basic structure of flavonoids) enhances the hydrophobicity of the molecule and thus its biological properties. This facilitates the interaction of flavonoids with the biofilm and their uptake by bacteria across the membrane, which enhances the inhibitory effects of flavonoids on the growth and biofilm formation of *P. gingivalis*. Therefore, given the research reviewed, it is advisable that there be more research that can help and identify the specific targets of prenyl flavonoids in gingipains and the signaling pathways involved.

Fernandes et al[109] and Dioguardi et al[47] highlight the role of *P. gingivalis* in AD pathogenesis, showing its presence in brain tissues and its ability to induce chronic inflammation via cytokines like IL-1β, IL-6, and TNF-α. Liu et al[98] reinforces this connection, reporting a sixfold increase in AD risk in patients with *P. gingivalis* detected in the brain (OR = 6.84, 95% CI: 2.70–17.31), while Rafiei M's[99] analysis of 49 studies identifies a strong association between *P. gingivalis* and PD (OR = 9.24, 95% CI: 5.78–14.77; $p < 0.0001$). Furthermore, Cunha et al[101] and Borsa et al[32] emphasize systemic inflammation as a key mediator, with cytokines such as IL-6 and TNF-α linking periodontitis to cognitive decline. Borsa[32] also reports a significant increase in *Fusobacterium nucleatum* in AD patients, supported by Liu's[98] findings of reduced oral microbiome diversity ($p < 0.00001$). While, Alshehri[102] finds no significant benefit in hyaluronic acid use for reducing *P. gingivalis* prevalence (OR = 0.95 at three months, 95% CI: 0.63–1.45; $p = 0.51$), the need for well-designed clinical trials remains crucial. Together, these studies underscore the complex interplay between oral pathogens, systemic inflammation, and neurodegeneration, calling for further research into preventive strategies targeting periodontal health to mitigate AD risk.

The increased presence of antibodies to *P. gingivalis* is associated with significantly impaired cognitive test scores in both animals and humans, based mainly on the fact that its cytotoxins, called gingipains, have the capacity to damage brain cells and contribute to neuroinflammation. These findings support the idea that *P. gingivalis* may play a central role in the onset and progression of Alzheimer's disease.

To better understand the relationship between periodontitis and Alzheimer's disease, longitudinal human studies are needed to track disease progression while accounting for confounding factors such as genetics and lifestyle. Randomized controlled trials should assess whether periodontal treatment can prevent or slow Alzheimer's progression. Additionally, advanced imaging and molecular techniques could clarify mechanisms like bacterial translocation, neuroinflammation, and amyloid plaque formation. Research on the gut-brain axis and salivary microbiota would also provide valuable insights into cognitive decline.

Current studies face limitations, including an over reliance on animal and in vitro models, which do not fully reflect human complexity. Many fail to address confounding factors like comorbidities and genetic predispositions. The mechanisms by which *P. gingivalis* induces neuroinflammation remain poorly explored, and there is an overfocus on select inflammatory markers. Lastly, the lack of long-term human research hinders establishing a definitive causal link between periodontitis and Alzheimer's disease.

Conclusion

Periodontitis not only affects oral health but also has important systemic consequences, and there is evidence of a potential link between periodontitis and neurodegenerative diseases, cardiovascular disease, diabetes and other conditions. For this reason, it is

crucial to recognize the importance of maintaining good periodontal health as part of overall health, thus driving the adoption of appropriate prevention and treatment strategies to mitigate the risk of systemic complications. Finally, it is important to note that despite ongoing research on the possible relationship between *P. gingivalis* and Alzheimer's disease, a definitive conclusion on its involvement in the pathogenesis of the disease has not yet been reached. However, the robust body of evidence presented in this review, which includes clinical, in vivo and in vitro studies, consistently points to a clear association between *P. gingivalis* and Alzheimer's disease. All the studies reviewed indicate a consistent relationship, highlighting the potential role of periodontal health in mitigating the risk of neurodegeneration. Further research should focus on establishing causality and elucidating the precise mechanisms involved to develop effective preventive and therapeutic strategies.

Acknowledgments

The authors thank the Universidad Católica de Cuenca, Cuenca, Ecuador, for its constant and timely support. Edisson-Mauricio Pacheco-Quito, Jéssica María Sarmiento-Ordóñez, are part of the Research Group: Innovación y Desarrollo Farmacéutico en Odontología, Facultad de Odontología, Jefatura de Investigación e Innovación, Universidad Católica de Cuenca, Cuenca, Ecuador.

Funding

The work was funded by the Universidad Católica de Cuenca, Cuenca, Ecuador, and is anchored to the research project called: "Eficacia antimicrobiana in vitro de sustancias no tradicionales frente a cepas microbianas de interés periodontopatógeno", approved under code: PIC5P23-61.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global prevalence of periodontal disease and lack of its surveillance. *Scientific World Journal*. 2020;2020:1–8. doi:10.1155/2020/2146160
2. O'Dwyer MC, Furgal A, Furst W, et al. The prevalence of periodontitis among US adults with multimorbidity using NHANES data 2011–2014. *Journal of the American Board of Family Medicine*. 2023;36(2):313–324. doi:10.3122/jabfm.2022.220207R1
3. Papapanou PN, Susin C. Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both? *Periodontol 2000*. 2017;75(1):45–51. doi:10.1111/prd.12200
4. Patel R. *The State of Oral Health in Europe Report Commissioned by the Platform for Better Oral Health in Europe*. 2012.
5. Zini A, Mazor S, Timm H, et al. Effects of an oral hygiene regimen on progression of gingivitis/early periodontitis: a randomized controlled trial. *Can J Dent Hyg*. 2021;55:85.
6. Rodrigues WF, Miguel CB, Agostinho F, et al. Metabolomic evaluation of chronic periodontal disease in older adults. *Mediators Inflamm*. 2021;2021:1–8. doi:10.1155/2021/1796204
7. Nyorobi JM, Carneiro LC, Kabulwa MN. Knowledge and practices on periodontal health among adults, Misungwi, Tanzania. *Int J Dent*. 2018;2018:1–7. doi:10.1155/2018/7189402
8. Lavigne SE. The 2018 AAP/EFP classification of periodontal & peri-implant diseases. Available from: www.dentalcare.com/en–us/professional–education/ce–courses/ce610. Accessed March 14, 2025.
9. Hernández-Monjaraz B, Santiago-Osorio E, Ledesma-Martínez E, Aguiñiga-Sánchez I, Sosa-Hernández NA, Mendoza-Núñez VM. Dental pulp mesenchymal stem cells as a treatment for periodontal disease in older adults. *Stem Cells Int*. 2020;2020:1–12. doi:10.1155/2020/8890873
10. Rovai ES, Holzhausen M. The role of proteinase-activated receptors 1 and 2 in the regulation of periodontal tissue metabolism and disease. *J Immunol Res*. 2017;2017:1–13. doi:10.1155/2017/5193572
11. Carvalho-Filho PC, Moura-Costa LF, Pimentel ACM, et al. Apoptosis transcriptional profile induced by porphyromonas gingivalis HmuY. *Mediators Inflamm*. 2019;2019:1–8. doi:10.1155/2019/6758159
12. Pham TAV, Tran TTP, Luong NTM. Antimicrobial effect of platelet-rich plasma against porphyromonas gingivalis. *Int J Dent*. 2019;2019:1–6. doi:10.1155/2019/7329103
13. Sadrameli M, Bathini P, Alberi L. Linking mechanisms of periodontitis to Alzheimer's disease. *Curr Opin Neurol*. 2020;33(2):230–238. doi:10.1097/WCO.0000000000000797
14. Singhrao SK, Olsen I. Assessing the role of porphyromonas gingivalis in periodontitis to determine a causative relationship with Alzheimer's disease. *J Oral Microbiol*. 2019;11(1):1563405. doi:10.1080/20002297.2018.1563405
15. Pazos P, Leira Y, Domínguez C, Pías-Peleteiro JM, Blanco J, Aldrey JM. Association between periodontal disease and dementia: a literature review. *Neurologia*. 2018;33(9):602–613. doi:10.1016/j.nrl.2016.07.013
16. Mendiola-Precoma J, Berumen LC, Padilla K, Garcia-Alcocer G. Therapies for prevention and treatment of Alzheimer's disease. *Biomed Res Int*. 2016;2016:1–17. doi:10.1155/2016/2589276

17. Cremonini AL, Caffa I, Cea M, Nencioni A, Odetti P, Monacelli F. Nutrients in the Prevention of Alzheimer's Disease. *Oxid Med Cell Longev*. 2019;2019:1–20. doi:10.1155/2019/9874159
18. Leshchyns'Ka I, Sytnyk V. Synaptic cell adhesion molecules in Alzheimer's disease. *Neural Plast*. 2016;2016:1–9. doi:10.1155/2016/6427537
19. Anggono V, Tsai LH, Götz J. Glutamate receptors in Alzheimer's disease: mechanisms and therapies. *Neural Plast*. 2016;2016:1–2. doi:10.1155/2016/8256196
20. Sumsuzzman DM, Uddin MS, Kabir MT, et al. Microglia in Alzheimer's disease: a favorable cellular target to ameliorate Alzheimer's pathogenesis. *Mediators Inflamm*. 2022;2022:1–17. doi:10.1155/2022/6052932
21. Magi S, Castaldo P, MacRi ML, et al. Intracellular calcium dysregulation: implications for Alzheimer's disease. *Biomed Res Int*. 2016;2016:1–14. doi:10.1155/2016/6701324
22. Meng Z, Chen H, Deng C, Meng S. Multiple roles of paeoniflorin in alzheimer's disease. *Evid Based Complement Alternat Med*. 2022;2022:1–11. doi:10.1155/2022/2464163
23. Beydoun MA, Beydoun HA, Hossain S, El-Hajj ZW, Weiss J, Zonderman AB. Clinical and bacterial markers of periodontitis and their association with incident all-cause and Alzheimer's disease dementia in a large national survey. *Journal of Alzheimer's Disease*. 2020;75 (1):157–172. doi:10.3233/jad-200064
24. Alakkas A, Meyer A, Debbold E, Yagudayeva R, Bui J. Early-onset Alzheimer's disease masquerading as catatonia. *Case Rep Neurol Med*. 2020;2020:1–5. doi:10.1155/2020/1493481
25. El Haj M, Colombel F, Kapogiannis D, Gallouj K. False memory in Alzheimer's disease. *Behavioural Neurology*. 2020;2020:1–10. doi:10.1155/2020/5284504
26. Ryder MI, Xenoudi P. Alzheimer disease and the periodontal patient: new insights, connections, and therapies. *Periodontol 2000*. 2021;87 (1):32–42. doi:10.1111/prd.12389
27. Naseri NN, Wang H, Guo J, Sharma M, Luo W. The complexity of tau in Alzheimer's disease. *Neurosci Lett*. 2019;705:183–194. doi:10.1016/j.neulet.2019.04.022
28. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int J Nanomedicine*. 2019;14:5541–5554. doi:10.2147/IJN.S200490
29. Olsen I. Porphyromonas gingivalis-induced neuroinflammation in Alzheimer's disease. *Front Neurosci*. 2021;15. doi:10.3389/fnins.2021.691016
30. Gaur S, Agnihotri R. Alzheimer's disease and chronic periodontitis: is there an association? *Geriatr Gerontol Int*. 2015;15(4):391–404. doi:10.1111/ggi.12425
31. Singhrao SK, Harding A, Poole S, Kesavalu L, Crean SJ. Porphyromonas gingivalis periodontal infection and its putative links with Alzheimer's disease. *Mediators Inflamm*. 2015;2015. doi:10.1155/2015/137357
32. Borsa L, Dubois M, Sacco G, Lupi L. Analysis the link between periodontal diseases and Alzheimer's disease: a systematic review. *Int J Environ Res Public Health*. 2021;18(17):9312. doi:10.3390/ijerph18179312
33. Beydoun MA, Beydoun HA, Weiss J, Hossain S, El-Hajj ZW, Zonderman AB. Helicobacter pylori, periodontal pathogens, and their interactive association with incident all-cause and Alzheimer's disease dementia in a large national survey. *mol Psychiatry*. 2021;26(10):6038–6053. doi:10.1038/s41380-020-0736-2
34. Gongora-Rivera F, Cordero-Perez A, Gonzalez-Aquines A, et al. Impaired cerebral vasomotor reactivity in Alzheimer's disease. *Int J Alzheimers Dis*. 2018;2018. doi:10.1155/2018/9328293
35. Penido AB, De Morais SM, Ribeiro AB, et al. Medicinal plants from northeastern Brazil against Alzheimer's disease. *Evid Based Complement Alternat Med*. 2017;2017. doi:10.1155/2017/1753673
36. Magalingam KB, Radhakrishnan A, Ping NS, Haleagrahara N. Current concepts of neurodegenerative mechanisms in Alzheimer's disease. *Biomed Res Int*. 2018;2018:1–12. doi:10.1155/2018/3740461
37. Hernández AE, García E. Mesenchymal stem cell therapy for Alzheimer's disease. *Stem Cells Int*. 2021;2021:1–12. doi:10.1155/2021/7834421
38. Ide M, Harris M, Stevens A, et al. Periodontitis and cognitive decline in Alzheimer's disease. *PLoS One*. 2016;11(3):e0151081. doi:10.1371/journal.pone.0151081
39. Liang Y, Xie S, He Y, et al. Kynurenine pathway metabolites as biomarkers in Alzheimer's disease. *Dis Markers*. 2022;2022:1–15. doi:10.1155/2022/9484217
40. D'Onofrio G, Yu Z, Forlenza OV. Alzheimer's disease and cognitive frailty: novel therapeutic technologies. *Biomed Res Int*. 2016;2016:1–2. doi:10.1155/2016/7242651
41. Leira Y, Domínguez C, Seoane J, et al. Is periodontal disease associated with Alzheimer's disease? A systematic review with meta-analysis. *Neuroepidemiology*. 2017;48(1–2):21–31. doi:10.1159/000458411
42. Teixeira FB, Saito MT, Matheus FC, et al. Periodontitis and Alzheimer's disease: a possible comorbidity between oral chronic inflammatory condition and neuroinflammation. *Front Aging Neurosci*. 2017;9. doi:10.3389/fnagi.2017.00327
43. Bertoa MF, Moreno N, Perez-Vereda A, Bandera D, Álvarez-Palomo JM, Canal C. Digital avatars: promoting independent living for older adults. *Wirel Commun Mob Comput*. 2020;2020:1–11. doi:10.1155/2020/8891002
44. Wang YR, Lee HF, Hsieh PL, Chen CM. Development of the healthy aging perspectives questionnaire among older adults with chronic disease in Taiwan. *Health Soc Care Community*. 2023;2023:1–12. doi:10.1155/2023/8238748
45. Bazargan M, Smith J, Movassaghi M, et al. Polypharmacy among underserved older African American adults. *J Aging Res*. 2017;2017:1–8. doi:10.1155/2017/6026358
46. Shakeel MK, Goghari VM. Measuring fluid intelligence in healthy older adults. *J Aging Res*. 2017;2017:1–6. doi:10.1155/2017/8514582
47. Dioguardi M, Crincoli V, Laino L, et al. The role of periodontitis and periodontal bacteria in the onset and progression of Alzheimer′s disease: a systematic review. *J Clin Med*. 2020;9(2):495. doi:10.3390/jcm9020495
48. Leblhuber F, Huemer J, Steiner K, Gostner JM, Fuchs D. Knock-on effect of periodontitis to the pathogenesis of Alzheimer's disease? *Wien Klin Wochenschr*. 2020;132(17–18):493–498. doi:10.1007/s00508-020-01638-5
49. Matsushita K, Yamada-Furukawa M, Kurosawa M, Shikama Y. Periodontal disease and periodontal disease-related bacteria involved in the pathogenesis of Alzheimer's disease. *J Inflamm Res*. 2020;13:275–283. doi:10.2147/JIR.S255309

50. Luo K, Ma S, Guo J, Huang Y, Yan F, Xiao Y. Association between postmenopausal osteoporosis and experimental periodontitis. *Biomed Res Int*. 2014;2014:1–7. doi:10.1155/2014/316134
51. Pereira LL, Veiga Siqueira Amorim D, Brito Sampaio W, et al. Factors associated with periodontitis in patients with and without HIV. *Int J Dent*. 2023;2023:1–13. doi:10.1155/2023/9929835
52. Lai PC, Walters JD. Resolution of Localized Chronic Periodontitis Associated with Longstanding Calculus Deposits. *Case Rep Dent*. 2014;2014:1–6. doi:10.1155/2014/391503
53. De Andrade KQ, Almeida-Da-Silva CLC, Coutinho-Silva R. Immunological pathways triggered by porphyromonas gingivalis and Fusobacterium nucleatum: therapeutic possibilities. *Mediators Inflamm*. 2019;2019:1–20. doi:10.1155/2019/7241312
54. Holmer J, Eriksdotter M, Schultzberg M, Pussinen PJ, Buhlin K. Association between periodontitis and risk of Alzheimer′s disease, mild cognitive impairment and subjective cognitive decline: a case–control study. *J Clin Periodontol*. 2018;45(11):1287–1298. doi:10.1111/jcpe.13016
55. Hirasawa M, Kurita-Ochiai T. Porphyromonas gingivalis induces apoptosis and autophagy via ER stress in human umbilical vein endothelial cells. *Mediators Inflamm*. 2018;2018:1–8. doi:10.1155/2018/1967506
56. Patel M, Naidoo R, Owotade FJ. Inhibitory effect of dodonaea viscosa var. angustifolia on the virulence properties of the oral pathogens streptococcus mutans and porphyromonas gingivalis. *Evid Based Complement Alternat Med*. 2013;2013:1–5. doi:10.1155/2013/624089
57. Carvalho-Filho PC, Gomes-Filho IS, Meyer R, Olczak T, Xavier MT, Trindade SC. Role of porphyromonas gingivalis hmuy in immunopathogenesis of chronic periodontitis. *Mediators Inflamm*. 2016;2016:1–9. doi:10.1155/2016/7465852
58. Alqatami H, Said KN, Ammar AA, Nazzal H. Periodontitis and intra-oral plasmacytosis in a noonan's syndrome patient. *Genet Res*. 2022;2022. doi:10.1155/2022/1379769
59. Kaldas M, Barghorn A, Schmidlin PR. Actinomycosis as a rare local manifestation of severe periodontitis. *Case Rep Dent*. 2020;2020. doi:10.1155/2020/5961452
60. Lei S, Li J, Yu J, et al. Porphyromonas gingivalis bacteremia increases the permeability of the blood-brain barrier via the Mfsd2a/Caveolin-1 mediated transcytosis pathway. *Int J Oral Sci*. 2023;15(1). doi:10.1038/s41368-022-00215-y
61. Kamer AR, Craig RG, Niederman R, Fortea J, de Leon MJ. Periodontal disease as a possible cause for Alzheimer's disease. *Periodontol 2000*. 2020;83(1):242–271. doi:10.1111/prd.12327
62. Nero H, Franzén E, Ståhle A, Wallén MB, Hagströmer M. Long-term effects of balance training on habitual physical activity in older adults with parkinson's disease. *Parkinsons Dis*. 2019;2019. doi:10.1155/2019/8769141
63. Kariu T, Nakao R, Ikeda T, Nakashima K, Potempa J, Imamura T. Inhibition of gingipains and porphyromonas gingivalis growth and biofilm formation by prenyl flavonoids. *J Periodontal Res*. 2017;52(1):89–96. doi:10.1111/jre.12372
64. Miklos AC, Li C, Sorrell CD, Lyon LA, Pielak GJ. An upper limit for macromolecular crowding effects. *BMC Biophys*. 2011;4(1). doi:10.1186/2046-1682-4-13
65. Yoneda M, Suzuki N, Masuo Y, et al. Effect of S-PRG eluate on biofilm formation and enzyme activity of oral bacteria. *Int J Dent*. 2012;2012:1–6. doi:10.1155/2012/814913
66. Ramos D, Moromi N, Martínez E. Porphyromonas gingivalis: patógeno predominante en la periodontitis crónica [Porphyromonas gingivalis: predominant pathogen in chronic periodontitis]. *Revistas de investigación UNMSM*. 2011.
67. Taylor JJ. Protein biomarkers of periodontitis in saliva. *ISRN Inflamm*. 2014;2014:1–18. doi:10.1155/2014/593151
68. Nemoto TK, Ohara-Nemoto Y. Exopeptidases and gingipains in porphyromonas gingivalis as prerequisites for its amino acid metabolism. *Japanese Dental Science Review*. 2016;52(1):22–29. doi:10.1016/j.jdsr.2015.08.002
69. Leong XF, Ng CY, Badiah B, Das S. Association between hypertension and periodontitis: possible mechanisms. *The Scientific World Journal*. 2014;2014:1–11. doi:10.1155/2014/768237
70. Liu Z, Liu Y, Song Y, Zhang X, Wang S, Wang Z. Systemic oxidative stress biomarkers in chronic periodontitis: a meta-analysis. *Dis Markers*. 2014;2014:1–10. doi:10.1155/2014/931083
71. Devanoorkar A, Kathariya R, Guttiganur N, Gopalakrishnan D, Bagchi PR. A potential biomarker for periodontitis influenced diabetes mellitus and diabetes induced periodontitis. *Dis Markers*. 2014;2014:1–7. doi:10.1155/2014/930206
72. Laine ML, Loos BG, Crielaard W. Gene polymorphisms in chronic periodontitis. *Int J Dent*. 2010;2010:1–22. doi:10.1155/2010/324719
73. Nogueira AVB, Chaves De Souza JA, De Molon RS, et al. HMGB1 localization during experimental periodontitis. *Mediators Inflamm*. 2014;2014:1–10. doi:10.1155/2014/816320
74. Hienz SA, Paliwal S, Ivanovski S. Mechanisms of bone resorption in periodontitis. *J Immunol Res*. 2015;2015:1–10. doi:10.1155/2015/615486
75. Jabri B, Iken M, Achmit M, Rida S, Ennibi OK. Occurrence of candida albicans in periodontitis. *Int J Dent*. 2021;2021:1–7. doi:10.1155/2021/5589664
76. Choi S, Kim K, Chang J, et al. Association of chronic periodontitis on Alzheimer's disease or vascular dementia. *J Am Geriatr Soc*. 2019;67(6):1234–1239. doi:10.1111/jgs.15828
77. Sansores-España D, Carrillo-Avila A, Melgar-Rodriguez S, Díaz-Zuñiga J, Martínez-Aguilar V. Periodontitis and alzheimers disease. *Med Oral Patol Oral Cir Bucal*. 2021;26(1):e43–e48. doi:10.4317/medoral.23940
78. Romero I, Velázquez P, Pestana A. Periodontitis y Alzheimer: posibles mecanismos de vinculación [Periodontitis and Alzheimer's: possible linking mechanisms]. *Fundación Juan José Carraro*. 2021.
79. Nissrin B, Basma R, Majid S. Association between periodontitis and pulp calcifications: radiological study. *Int J Dent*. 2022;2022:1–8. doi:10.1155/2022/9599554
80. Hoare A, Soto C, Rojas-Celis V, Bravo D. Chronic inflammation as a link between periodontitis and carcinogenesis. *Mediators Inflamm*. 2019;2019:1–14. doi:10.1155/2019/1029857
81. Borgo Sarmento E, Lima Ribeiro Andrade Helena Teixeira R D, Cristina Gomes C, et al. Proinflammatory cytokine expression in apical periodontitis from diabetic patients. *Int J Dent*. 2023;2023:1–6. doi:10.1155/2023/4961827
82. Byun SH, Yoo DM, Chang M, Choi HG, Hong SJ. Relationship between periodontitis and glaucoma: a cross-sectional study. *J Ophthalmol*. 2020;2020:1–7. doi:10.1155/2020/5384602
83. Ding Y, Ren J, Yu H, Yu W, Zhou Y. Porphyromonas gingivalis, a periodontitis causing bacterium, induces memory impairment and age-dependent neuroinflammation in mice. *Immunity and Ageing*. 2018;15(1). doi:10.1186/s12979-017-0110-7
84. Zhao C, Kuraji R, Ye C, et al. Nisin a probiotic bacteriocin mitigates brain microbiome dysbiosis and Alzheimer's disease-like neuroinflammation triggered by periodontal disease. *J Neuroinflammation*. 2023;20(1). doi:10.1186/s12974-023-02915-6

85. Lee YT, Lee HC, Hu CJ, et al. Periodontitis as a modifiable risk factor for dementia: a nationwide population-based cohort study. *J Am Geriatr Soc*. 2017;65(2):301–305. doi:10.1111/jgs.14449
86. Chen CK, Wu YT, Chang YC. Association between chronic periodontitis and the risk of Alzheimer's disease: a retrospective, population-based, matched-cohort study. *Alzheimers Res Ther*. 2017;9(1). doi:10.1186/s13195-017-0282-6
87. Delwel S, Binnekade TT, Perez RSGM, Hertogh CMPM, Scherder EJA, Lobbezoo F. Oral hygiene and oral health in older people with dementia: a comprehensive review with focus on oral soft tissues. *Clin Oral Investig*. 2018;22(1):93–108. doi:10.1007/s00784-017-2264-2
88. Dominy E, Lynch C, Ermini F, et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv*. 2019.
89. Mysak J, Podzimek S, Sommerova P, et al. Porphyromonas gingivalis: major periodontopathic pathogen overview. *J Immunol Res*. 2014;2014:1–8. doi:10.1155/2014/476068
90. Lu J, Zhang S, Huang Y, et al. Periodontitis-related salivary microbiota aggravates Alzheimer's disease via gut-brain axis crosstalk. *Gut Microbes*. 2022;14(1). doi:10.1080/19490976.2022.2126272
91. Ilievski V, Zuchowska PK, Green SJ, et al. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. *PLoS One*. 2018;13(10):e0204941. doi:10.1371/journal.pone.0204941
92. Ishida E, Furusho H, Renn TY, et al. Mouse maternal odontogenic infection with porphyromonas gingivalis induces cognitive decline in offspring. *Front Pediatr*. 2023:11. doi:10.3389/fped.2023.1203894
93. Morikawa T, Uehara O, Paudel D, et al. Systemic administration of lipopolysaccharide from porphyromonas gingivalis decreases neprilysin expression in the mouse hippocampus. *In Vivo*. 2023;37(1):163–172. doi:10.21873/invivo.13065
94. Chi L, Cheng X, Lin L, et al. Porphyromonas gingivalis-induced cognitive impairment is associated with gut dysbiosis, neuroinflammation, and glymphatic dysfunction. *Front Cell Infect Microbiol*. 2021:11. doi:10.3389/fcimb.2021.755925
95. Haditsch U, Roth T, Rodriguez L, et al. Alzheimer's disease-like neurodegeneration in porphyromonas gingivalis infected neurons with persistent expression of active gingipains. *Journal of Alzheimer's Disease*. 2020;75(4):1301–1317. doi:10.3233/JAD-200393
96. Carter CJ, France J, Crean SJ, Singhrao SK. The porphyromonas gingivalis/host Interactome shows enrichment in GWASdb genes related to Alzheimer's disease, diabetes and cardiovascular diseases. *Front Aging Neurosci*. 2017;9(DEC). doi:10.3389/fnagi.2017.00408
97. Laugisch O, Johnen A, Maldonado A, et al. Periodontal pathogens and associated intrathecal antibodies in early stages of Alzheimer's disease. *J Alzheimers Dis*. 2018;66(1):105–114. doi:10.3233/JAD-180620
98. Liu S, Dashper SG, Zhao R, Yu JT. Association between oral bacteria and Alzheimer's disease: a systematic review and meta-analysis. *Journal of Alzheimer's Disease*. 2023;91(1):129–150. doi:10.3233/JAD-220627
99. Rafiei M, Kiani F, Sayehmiri F, Sayehmiri K, Sheikhi A, Azodi MZ. Study of porphyromonas gingivalis in periodontal diseases: a systematic review and meta-analysis. *Med J Islam Repub Iran*. 2017;31(1):355–362. doi:10.18869/mjiri.31.62
100. Fiorillo L, Cervino G, Laino L, et al. Porphyromonas gingivalis, periodontal and systemic implications: a systematic review. *Dent J*. 2019;7(4):114. doi:10.3390/dj7040114
101. Nascimento PC, Castro MML, Magno MB, et al. Association between periodontitis and cognitive impairment in adults: a systematic review. *Front Neurol*. 2019;10:10. doi:10.3389/fneur.2019.00323
102. Alshehri FA, Alharbi MS. The effect of adjunctive use of hyaluronic acid on prevalence of porphyromonas gingivalis in subgingival biofilm in patients with chronic periodontitis: a systematic review. *Pharmaceutics*. 2023;15(7):1883. doi:10.3390/pharmaceutics15071883
103. Lorenzi C, Lorenzi C, Bianchi N, Pinto A, Mazzetti V, Arcuri C. The role of periodontal bacteria, Porphyromonas Gingivalis, in Alzheimer's disease pathogenesis and aggravation: a review. 2021;35:37–45.
104. Bregaint S, Boyer E, Fong SB, Meuric V, Bonnaure-Mallet M, Jolivet-Gougeon A. Porphyromonas gingivalis outside the oral cavity. *Odontology*. 2022;110(1):1–19. doi:10.1007/s10266-021-00647-8
105. Li W, Zhu Y, Singh P, Ajmera DH, Song J, Ji P. Association of common variants in MMPs with periodontitis risk. *Dis Markers*. 2016;2016:1–20. doi:10.1155/2016/1545974
106. Takeuchi H, Nakamura E, Yamaga S, Amano A. Porphyromonas gingivalis infection induces lipopolysaccharide and peptidoglycan penetration through gingival epithelium. *Frontiers in Oral Health*. 2022;3. doi:10.3389/froh.2022.845002
107. Li X, Kiprowska M, Kansara T, Kansara P, Li P. Neuroinflammation: a distal consequence of periodontitis. *J Dent Res*. 2022;101(12):1441–1449. doi:10.1177/00220345221102084
108. Xu W, Zhou W, Wang H, Liang S. Roles of porphyromonas gingivalis and its virulence factors in periodontitis. *Adv Protein Chem Struct Biol*. 2020;120:45–84. doi:10.1016/bs.apcsb.2019.12.001
109. Fernandes Costa MJ, Dantas I, Araújo TD, et al. Relationship of porphyromonas gingivalis and alzheimer's disease: a systematic review of pre-clinical studies. 2021;25:797–806. doi:10.1007/s00784-020-03764-w/Published