



GRADUATION PROJECT

Degree in Dentistry

PERIODONTAL DISEASE AND ALZHEIMER'S

Madrid, academic year 2024/2025

Identification number: 163

RESUMEN

Introducción: La enfermedad periodontal (EP) es una afección inflamatoria oral muy extendida que afecta al 60% de las personas mayores de 65 años. La enfermedad de Alzheimer (EA), un trastorno neurodegenerativo progresivo caracterizado por la pérdida de memoria y el deterioro cognitivo, carece actualmente de cura. Ambas afecciones están relacionadas con la edad y comparten vías inflamatorias, lo que suscita un creciente interés en su posible conexión.

Objetivos: Esta revisión examina sistemáticamente si los patógenos de la EP contribuyen a la neuroinflamación implicada en la EA.

Metodología: Se realizó una revisión sistemática de estudios originales (2020-2025) utilizando MEDLINE Complete. Los estudios incluidos se centraron en la investigación animal, celular y clínica que investiga los vínculos entre los patógenos periodontales específicos y los mecanismos neuroinflamatorios en la EA. Sólo se incluyeron estudios de texto completo en inglés que abordaran explícitamente la neuroinflamación relacionada con la EA; se excluyeron las revisiones y los estudios cognitivos generales.

Resultados: Se clasificaron 28 estudios en cuatro grupos mecanicistas. Los hallazgos clave destacan que *P. gingivalis* y sus vesículas inducen la activación microglial M1 y la liberación de citoquinas proinflamatorias (IL-1 β , TNF- α), perjudicando la función neuronal. La inflamación causada por patógenos inhibió la desfosforilación de tau y elevó los niveles de A β 42, características fundamentales de la patología de la EA. La infección alteró la integridad de la barrera hematoencefálica a través del daño endotelial y el aumento de endotelina-1. Además, los desequilibrios microbianos relacionados con *P. gingivalis* en la microbiota oral e intestinal se relacionaron con biomarcadores de EA en líquido cefalorraquídeo, lo que respalda aún más el papel microbiano en la neuroinflamación.

Conclusiones: La inflamación crónica por patógenos periodontales parece exacerbar la neuroinflamación, contribuyendo a la progresión de la EA. Estos hallazgos enfatizan la relevancia de la salud oral en la prevención de enfermedades sistémicas y ofrecen vías prometedoras para la intervención terapéutica dirigida a los mecanismos relacionados con la EP en la EA.

PALABRAS CLAVE

Odontología, enfermedad periodontal, enfermedad de alzheimer, neuroinflamación, *Porphyromonas gingivalis*

ABSTRACT

Introduction: Periodontal disease (PD) is a widespread oral inflammatory condition affecting 60% of individuals over age 65. Alzheimer's disease (AD), a progressive neurodegenerative disorder marked by memory loss and cognitive decline, currently lacks a cure. Both conditions are age-related and share inflammatory pathways, prompting growing interest in their potential connection.

Objectives: This review systematically examines whether PD pathogens contribute to neuroinflammation implicated in AD.

Methodology: A systematic review of original studies (2020–2025) was conducted using MEDLINE Complete. Included studies focused on animal, cellular, and clinical research investigating links between specific periodontal pathogens and neuroinflammatory mechanisms in AD. Only English-language, full-text studies explicitly addressing AD-related neuroinflammation were included; reviews and general cognitive studies were excluded.

Results: Twenty-eight studies were categorized into four mechanistic groups. Key findings highlight that *P. gingivalis* and its vesicles induce M1 microglial activation and pro-inflammatory cytokine release (IL-1 β , TNF- α), impairing neural function. Pathogen-driven inflammation inhibited tau dephosphorylation and elevated A β 42 levels—core features of AD pathology. Infection disrupted blood-brain barrier integrity via endothelial damage and increased endothelin-1. Additionally, microbial imbalances involving *P. gingivalis* in oral and gut microbiota were linked with cerebrospinal fluid AD biomarkers, further supporting a microbial role in neuroinflammation.

Conclusions: Chronic inflammation from periodontal pathogens appears to exacerbate neuroinflammation, contributing to AD progression. These findings emphasize oral health's relevance in systemic disease prevention and offer promising avenues for therapeutic intervention targeting PD-related mechanisms in AD.

KEYWORDS

Dentistry, periodontal disease, alzheimer's disease, neuroinflammation, *Porphyromonas gingivalis*

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1. INTRODUCTION

1.1. General

Periodontal disease (PD) is the second most common oral disease behind caries and is the leading cause of tooth loss in adults (1). PD is an inflammatory condition of the gingiva, periodontal ligament, cementum, and alveolar bone, primarily caused by the persistent presence of bacterial biofilms in the subgingival environment (2). Periodontitis is considered an age-related disease with a global prevalence of about 5% in individuals aged 35 years or younger, 50% in those aged 45 years, and 60% in individuals over 45 years (3,4). According to the World Health Organization (WHO), the total global expenditure on oral diseases in 2019 was estimated to be \$387 billion and PD accounting for a big percentage of it (5). Research over the years has shown that chronic systemic inflammation caused by oral bacteria is not only linked to periodontal disease but has an effect in distant parts of the body causing cardiovascular disease, rheumatoid arthritis, metabolic syndromes, autoimmune diseases, and Alzheimer's disease (AD) (6). AD is the most common form of dementia characterized by progressive cognitive decline, memory loss, and impairment of physical functions. It was reported that the global cost of treating and taking care of people with AD was \$ 1.3 trillion USD, therefore this substantial amount is a significant concern as the prevalence of the disease is expected to rise (7). Like periodontal disease, AD is an age-related disease and with life expectancy increasing there will be more people who are at a higher risk of developing both of these diseases. An increasing amount of evidence suggests that periodontal disease has the capacity to cause neuroinflammation which is a key pathogenic connector to neurodegenerative diseases such as AD. Consequently, there is a growing interest in discovering new approaches to prevent and/or treat Alzheimer's disease by addressing periodontal disease.

1.2. Periodontal Disease

Periodontal disease is a complex oral condition that encompasses a spectrum of inflammatory and infectious processes, ranging from the milder form of gingivitis to the more severe periodontitis (8). The etiology of PD is multifactorial, including the presence of bacterial biofilm, host immune-inflammatory response, modifiable risk factors, and non-modifiable risk factors(8). The common modifiable risk factors include smoking tobacco, poor oral hygiene, diabetes mellitus, and pregnancy play a crucial role in PD development. Despite this, the most significant impact on management of PD is the treatment of these risk factors (8). Periodontal disease commonly starts with the deposit of bacterial plaque also known as biofilm along the gingival margin and is dependent on the immune response of the patient (8). Gingivitis is the first and only stage that is reversible, defined by local inflammation causing redness, swelling, increase in probing depth, bleeding of the gingiva with no attachment loss or alveolar bone destruction (9). The common symptoms of gingivitis coupled with the often painless nature of the condition, can lead an accustomed individual to overlook this stage and allow the

progression to periodontitis. When gingivitis is untreated and proper oral hygiene is not maintained, the accumulation of biofilm will advance subgingivally allowing the proliferation of Gram-negative anaerobic bacteria to cause the progression of the disease to periodontitis. Periodontitis is the irreversible form of the disease causing a systemic inflammatory reaction which affects the deeper periodontal tissues causing periodontal pockets, loss of connective tissue attachment, tooth mobility, gingival recession, and bone loss ultimately resulting in tooth loss (9). The understanding of each stage of the disease allows us to understand the level of damage and immune response involved. The characteristic of chronic periodontal inflammation is the constant presence of subgingival plaque in the gingival sulcus causing a constant discharge of destructive inflammatory cells (10). The current method of diagnosis for periodontal disease is a multidimensional approach involving staging and grading to assess severity and risk of progression yet there is still no cure. Staging ranges from stage I (initial) to stage IV (advanced) primarily using clinical attachment loss and radiographic bone loss as the key parameters. Grading ranges from Grade A to Grade C assessing the risk of disease progression considering factors like direct and indirect evidence of progression rate, risk factors, and systemic factors (11). Systemic factors being considered in the grading of periodontal disease proves that there is a link between the oral cavity and body as a system.

1.3. Key Periodontal Pathogens

The complex microbial ecosystem of the oral cavity contains approximately 800 species of bacteria that are in symbiosis with a healthy host while in a pathological state such as periodontal disease, the bacteria are in a dysbiosis causing a proliferation of highly pathogenic bacteria (4,6). The most putative bacteria that have been identified in PD includes *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia*, and *Fusobacterium nucleatum* (12). The formation of this biofilm begins with the adherence of bacteria to the tooth surface, which then leads to the colonization and growth of these various bacterial species. As the biofilm matures, it becomes more complex, with different bacterial species occupying distinct spatial niches and interacting with each other through a variety of mechanisms. Initially, the biofilm consists mostly of Gram-positive cocci bacteria, but as it matures, it shifts to include more pathogenic Gram-negative species.

1.4. Alzheimer's Disease

Alzheimer's disease is a prevalent and devastating neurodegenerative disorder that primarily affects the population over 65 years old yet without a cure. According to statistics, almost two thirds of all AD cases are women affecting a staggering 4.1 million women and 2.6 million men over the age of 65 in the USA (13). The debilitating symptoms of Alzheimer's disease are characterized by memory loss, affected comprehension, language loss, inability to communicate, inability to continue working, and inability to take care of oneself (14). According to reported global statistics, the prevalence of dementia surged from 20.2 million in 1990 to 58 million in 2022 which is a staggering 187% increase over 32 years. This upward trend is expected to continue, with projections estimating between 82 and 150 million cases by 2050 (13,15). As dementia cases rise, the strain on healthcare systems is intensifying, with the global

number of affected individuals doubling or even tripling in the next 30 years. According to data reported by the Alzheimer's Association, AD was the 5th leading cause of death for ages over 65 years old in the United States in 2023 (15). Although AD does not directly cause death, it significantly increases an individual's susceptibility to other complications that shortens their lifespan. The exact etiology of Alzheimer's disease is not fully understood, but it is believed to be a multifactorial condition involving a complex interplay of factors, including aging, genetic predisposition, environmental influences, modifiable factors, non-modifiable factors and immune system dysfunction (16,17).

The hallmark pathological features of Alzheimer's disease include the accumulation of amyloid-beta peptides and the formation of neurofibrillary tangles (NFT) composed of hyperphosphorylated tau proteins, which in turn lead to neuronal dysfunction, synaptic loss, and ultimately, brain atrophy and widespread neurodegeneration (14).

Advancements in research and technology now allow for the diagnosis of Alzheimer's disease before symptoms appear, whereas in the past, it could only be confirmed postmortem through brain dissection (13). The newest methods are able to detect changes in the brain based on: presence of amyloid-beta and tau proteins in cerebrospinal fluid or using a positron emission tomography to show atrophic areas in the brain with accumulations of amyloid beta and tau proteins (16).

1.5. Neuroinflammation and Periodontitis

Neuroinflammation is considered one of the critical factors that leads to initiation and/or progression of AD (18). It has been shown that proinflammatory factors induced by chronic inflammation cause neural cell death (12). Chronic inflammation caused by periodontal bacteria has been linked as a potential risk factor in the onset and progression of Alzheimer's disease, as studies have shown that chronic systemic inflammation is associated with neuroinflammation, which can lead to neurodegeneration (12). The constant inflammatory state leads to elevation of proinflammatory cytokines which includes interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), matrix metalloproteinases (MMPs), reaction oxygen species (ROS), and neuropeptides some of which have been shown to cross the blood-brain barrier (19). Interestingly, data shows that people with dementia have increased levels of C-reactive protein (CRP), IL-1 β and IL-6, and TNF- α which are also increased in individuals with periodontal disease (12). During periodontitis, inflammatory mediators can enter the systemic circulation and create a state of chronic low-grade inflammation, which has been implicated in the pathogenesis of various systemic diseases, including Alzheimer's disease (18).

This inflammation can have a significant effect on people who have predispositions to Alzheimer's disease due to their familial genetics, mutations, age, and gender. The complement system is a crucial component of the innate immune system, designed to combat infections. However, research has demonstrated that excessive activation of the complement system can create an inflammatory microenvironment, leading to increased cell death (20). The disproportionate complement activity has been linked to changes in the structures such as appearance of A β plaques and changes in the blood-brain barrier function (20). Once

cytokines and bacteria cross the blood-brain-barrier, glial cells are activated producing cytokines which induce neuroinflammation. Microglial cells are the innate immune cells of the brain and central nervous system (CNS) and studies have shown that their overproduction of cytokines is typical in Alzheimer's patients. Over production of proinflammatory cytokines is also associated with the increased amyloid- β production (20). Even though bacterial plaque is accumulated in the oral cavity we can see that it exerts systemic effects through mechanisms involved in innate and adaptive immune responses.

2. OBJECTIVE

The objective of this literature review is to systematically explore and understand the possible ways periodontal disease pathogens contribute to neuroinflammation in Alzheimer's disease by evaluating recent evidence from molecular, clinical, and epidemiological studies.

3. MATERIAL AND METHODS

A systematic literature search was conducted using MEDLINE Complete to identify relevant scientific articles on the topic of "Periodontal Disease pathogens, neuroinflammation, and Alzheimer's Disease". The research aims to analyze the association between periodontal disease pathogens' role in causing neuroinflammation in Alzheimer's disease.

The inclusion criteria for assembling the results section were selected based on: studies published within the last 5 years (2020-2025) to ensure the use of up to date sources, full text format articles, and studies published in English. Articles were excluded if they mentioned cognitive decline or cognitive impairment without focusing on Alzheimer's disease. Only original research articles, including experimental, cross-sectional, cohort, and case control studies were considered if they focused on the connection between PD and AD through neuroinflammatory pathways. Any systematic literature reviews or review articles were excluded.

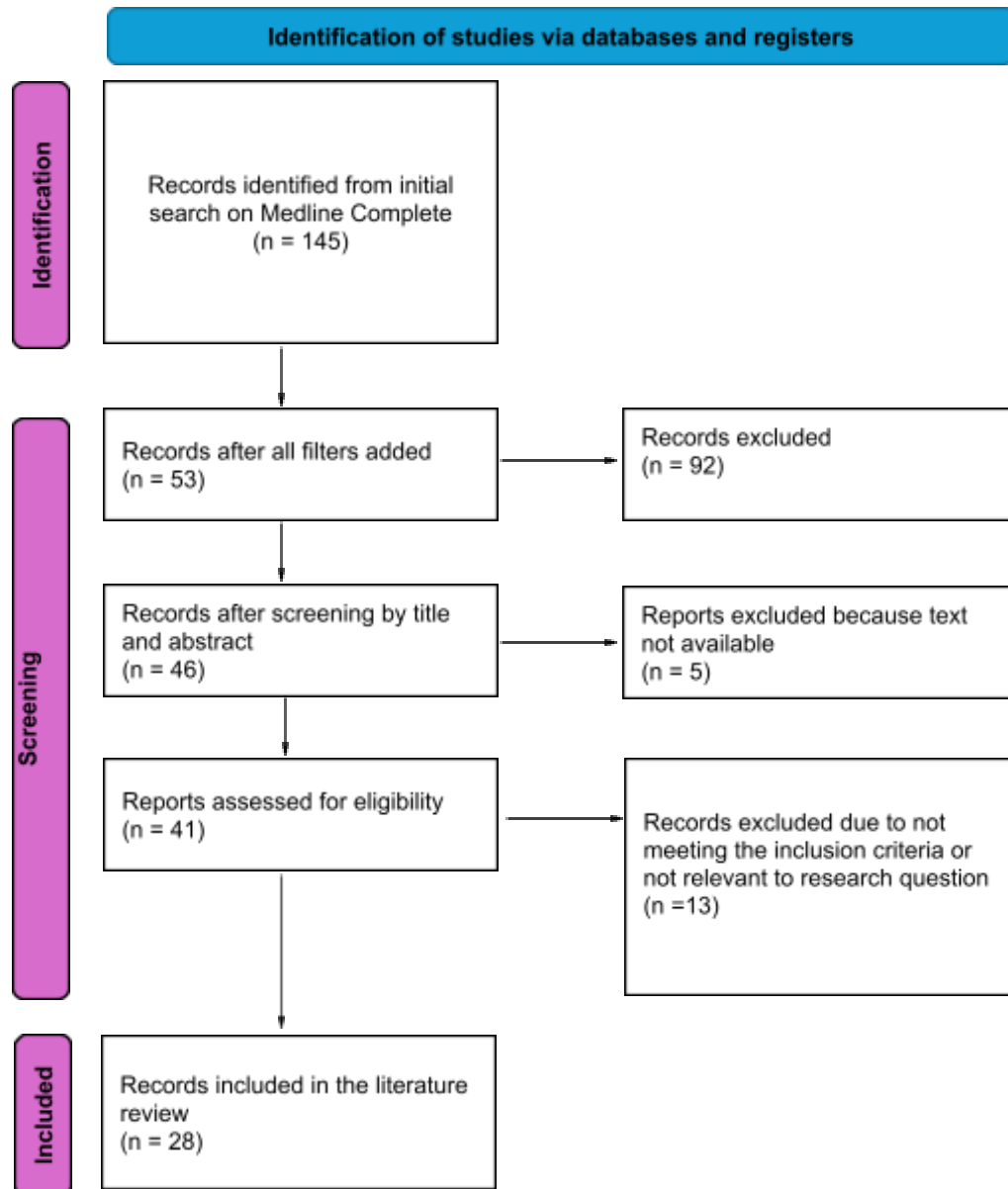
The search strategy was done using specific keywords and Boolean operators. The keywords and search equations were developed based on the PICO framework and combined using Boolean operators (AND, OR, NOT) to ensure comprehensive search.

Keywords and Boolean operators: ("periodontal disease" OR "periodontitis" OR "periodontal pathogens" OR "oral bacteria" OR "Porphyromonas gingivalis" OR "Aggregatibacter actinomycetemcomitans" OR "Treponema denticola" OR "Tannerella forsythia") AND ("neuroinflammation" OR "neurodegeneration" OR "brain inflammation" OR "microglial activation" OR "neuroimmune response") AND ("Alzheimer's disease" OR "dementia" OR "cognitive decline" OR "neurodegenerative disease")

A systematic review approach was chosen to synthesize the latest evidence, focusing on original research published in the last five years to ensure up-to-date and clinically relevant findings.

4. RESULTS

PRISMA 2000 Flow diagram for new systematic reviews which included searches of data bases, registers, and other sources (21)



The results of the literature review were added and summarized in Table 1. The 28 articles which met the selection criteria were analyzed and four different categories have been created based on the thematic focus of their objectives and outcomes to allow us to examine the data and outcomes of the studies. Each category included the results of articles that best suited the specific category.

Table 1. Review of Studies: Periodontal Disease and Neuroinflammation in Alzheimer's Disease

First Author & Date	Objective of Study	Type of Study & Population	Key Biomarkers/Cytokines/Chemokines	Results	Connection to Objective
Qiu et al. (2025) (22)	Investigate mechanisms by which <i>P. gingivalis</i> and its outer membrane vesicles (OMVs) contribute to neuroinflammation.	Animal study: mice	IL-1 β , TNF- α , IL-6, NLRP3 inflammasome activation, occludin.	<i>P. gingivalis</i> induced systemic inflammation and NLRP3 activation; OMVs disrupted BBB integrity, leading to neuroinflammation.	<i>P. gingivalis</i> and OMVs trigger neuroinflammation, supporting the hypothesis that periodontal pathogens contribute to neurodegeneration.
Magnusson et al. (2024) (23)	Examine how <i>P. gingivalis</i> and its lipopolysaccharides (LPS) influence microglial activation and neurodegenerative processes.	In vitro study	NOX4, IL-6, IL-8, total and phosphorylated tau (pTau), reactive oxygen species (ROS).	<i>P. gingivalis</i> LPS increased NOX4 expression in microglia, elevated ROS, and induced tau phosphorylation in neurons.	Demonstrates a pathway where <i>P. gingivalis</i> could drive neuroinflammation and neurodegeneration in AD.
Li et al. (2024) (24)	Investigate how <i>P. gingivalis</i> affects microglia via the NF- κ B signaling pathway.	Animal study: mice & in vitro study	IL-6, IL-17, IL-10, NF- κ B pathway markers.	<i>P. gingivalis</i> induced neuroinflammation by promoting M1 polarization of microglia via activation of the NF- κ B pathway.	Supports <i>P. gingivalis</i> -driven neuroinflammation in AD via microglial activation
Ciccotosto et al. (2024) (25)	Investigate if chronic oral inoculation of <i>P. gingivalis</i> and <i>T. denticola</i> induces Alzheimer's pathology.	Animal study: mice	IL-1 β , IL-6, Iba-1 (microglia activation), GFAP (astrocyte activation), Amyloid-beta plaques (A β), Hyperphosphorylated tau (pTau).	<i>P. gingivalis</i> significantly increased IL-1 β , IL-6, astrocyte and microglial activation; induced amyloid-beta plaques and tau hyperphosphorylation.	Demonstrates that periodontal pathogens induce neuroinflammation and Alzheimer's pathology in a mouse model.

Troci et al. (2024) (26)	Analyze microbiota changes in AD, focusing on changes between oral and fecal microbiota.	Human cross-sectional observational study (n=151)	Alterations in gut microbiota (Bacteroidetes, Porphyromonadaceae), Increased oral <i>P. gingivalis</i> , Neisseria.	Distinct gut and oral microbiota shifts in AD; increased <i>P. gingivalis</i> correlated with cerebrospinal fluid tau and amyloid burden.	Links oral <i>P. gingivalis</i> and systemic microbiome changes to neuroinflammation in AD.
Gui et al. (2024) (27)	To determine the effects of a natural ingredient mixture on microglial neurotoxic polarization.	In vitro study	IL-1 β , IL-6, TNF- α , IL-10, TGF β 1, BDNF, NF- κ B/Nrf2 activation, mitochondrial ROS production.	Natural ingredient mixture suppressed proinflammatory cytokines, enhanced anti-inflammatory markers (IL-10, TGF β 1), and improved mitochondrial function in microglia.	Indicates that natural compounds may mitigate neuroinflammation by altering microglial polarization and mitochondrial function.
Oue et al. (2024) (28)	Assess the impact of oral <i>P. gingivalis</i> infection on cognitive function and brain inflammation in obese mice.	Animal study: mice	IL-1 β , TNF- α , microglial activation markers.	<i>P. gingivalis</i> infection impaired cognitive function and increased neuroinflammation. Microglial depletion improved cognition.	Provides evidence that <i>P. gingivalis</i> contributes to cognitive dysfunction and neuroinflammation.
Verma et al. (2023) (29)	Investigate how <i>P. gingivalis</i> -LPS induces mitochondrial dysfunction and neuroinflammation.	In vitro study	A β 1-42, NO, iNOS, IL-1 β , IL-6, TNF- α , mitochondrial function markers.	<i>P. gingivalis</i> -LPS increased oxidative stress, neuroinflammatory markers, and mitochondrial dysfunction.	Proposes a mechanistic pathway linking periodontal infection to neurodegeneration via mitochondrial dysfunction.
Cheng et al. (2023) (30)	Determine if exogenous mMDSCs improve immune	Animal study: rats	A β , Iba1, IL-6, IL-10, IFN- γ	<i>P. gingivalis</i> worsened cognitive impairment and amyloid	Shows that <i>P. gingivalis</i> exacerbates AD neuroinflammation and

	imbalance, neuroinflammation, and cognitive impairment in mice infected with <i>P. gingivalis</i> .			deposition. mMDSCs restored immune balance, reduced neuroinflammation, and improved cognitive function	cognitive decline, while mMDSCs reverses these effects, supporting a causal role of pathogens in AD progression
Wang et al. (2023) (31)	Highlights roles of IL-1 β and TNF- α in the link between periodontitis and AD.	Animal study: mice	IL-1 β , TNF- α , CRP, GFAP, Iba1, pTau, A β , MCP-1	IL-1 β and TNF- α increased in periodontitis, exacerbated neuroinflammation, tau pathology, and cognitive decline in AD mice.	Establishes proinflammatory cytokines as mediators of neuroinflammation connecting periodontitis with AD progression.
Zhao et al. (2023) (32)	Examine the role of probiotic bacteriocin Nisin in modulating brain microbiome dysbiosis and neuroinflammation caused by periodontal disease.	Animal study: mice	IL-1 β , IL-6, TNF- α , amyloid- β 42 (A β 42), total tau, phosphorylated tau (pS199).	Nisin reduced brain microbiome dysbiosis, decreased inflammatory cytokines, and reduced amyloid and tau deposition.	Supports the therapeutic potential of probiotics in reducing periodontal-induced neuroinflammation in AD.
Ma et al. (2023) (33)	To assess how probiotics (<i>L. pentosus</i> and <i>B. bifidum</i>) can alleviate <i>P. gingivalis</i> induced neuroinflammation, periodontitis, and cognitive impairment in mice.	Animal study: mice	TNF- α , IL-1 β , IL-6, NF- κ B, BDNF, NMDAR, GP+Iba1+ cells in hippocampus.	Probiotics reduced neuroinflammatory markers, improved cognitive function, suppressed NF- κ B activation, and increased BDNF levels in the hippocampus.	Suggests that probiotics may have therapeutic effects against <i>P. gingivalis</i> -induced neuroinflammation and cognitive decline.
Almarhouni et	Assess microglial	Animal study: mice	TNF- α , IL-1 β , IL-6, Toll-like	Microglial activation and	Demonstrates direct activation

al. (2023) (34)	response to experimental PD and its impact on neuroinflammation.		receptors (TLR2, TLR9), phagocytic receptors.	increased pro-inflammatory cytokine expression were observed following periodontal disease induction.	of microglia by periodontal infection, relevant to neuroinflammation in AD.
Yamawaki et al. (2022) (35)	Investigate whether imipramine prevents <i>P. gingivalis</i> LPS-induced microglial neurotoxicity.	Animal study: mice	IL-1 β , TNF- α , NF- κ B signaling.	Imipramine reduced neuroinflammation, microglial activation, and neuronal cell death.	Suggests that imipramine can mitigate periodontal-induced neuroinflammation.
Duan et al. (2022) (36)	Assess the impact of experimental periodontitis on cognitive deficits in AD-induced rats.	Animal study: rats	Insulin signaling (Akt, GSK-3 β), IL-6, COX-2	Periodontitis exacerbated cognitive deficits in AD rats. Increased tau phosphorylation, glial activation, and IL-6/COX-2. Impaired insulin signaling and reduced neuronal survival.	Demonstrates that periodontitis worsens AD pathology by impairing insulin signaling, promoting neuroinflammation, and increasing tau pathology, linking PD to AD neuroinflammation.
Lecca et al. (2022) (37)	Examines if neuroinflammation synaptic/neuronal loss and cognitive decline in Alzheimer's disease.	Animal study: mice	TNF- α , IL-1 β , IL-6, GFAP, Iba1, A β , pTau	Neuroinflammation was linked to synapse loss and cognitive decline. Anti-inflammatory drug treatment improved cognition without affecting A β .	Demonstrates that neuroinflammation independently drives neurodegeneration and cognitive impairment in AD.
Hao et al. (2022)	Explore how periodontal infection	Animal study: mice	C1q, C3, IL-1 β , IL-6, TNF- α , Iba1, PSD95,	<i>P. gingivalis</i> infection increased C1q	Strong mechanistic link between

(38)	aggravates Alzheimer's pathology via C1q-mediated microglial activation and synapse pruning.		SNAP25, A β	expression, microglial activation, synapse loss, and A β burden, worsening Alzheimer's pathology.	periodontal infection and AD pathology via complement-mediated microglial activation.
Karaka ya et al. (2022) (39)	Investigate the impact of <i>P. gingivalis</i> infection on the endothelin (ET) system and cell senescence in brain microvascular endothelial cells (BMVECs).	In vitro study	Endothelin-1 (ET-1), ETA/ETB receptors, senescence markers (p16, p21, Lamin A/C), tight junction proteins (Occludin 1, Claudin 5).	<i>P. gingivalis</i> infection increased ET-1 secretion, upregulated ETA receptor expression, and reduced Lamin A/C and tight junction proteins, indicating compromised endothelial integrity.	Links <i>P. gingivalis</i> infection with endothelial dysfunction and potential blood-brain barrier compromise, which could contribute to neuroinflammation in AD
Chi et al. (2021) (40)	Assess if <i>P. gingivalis</i> induces cognitive impairment via gut dysbiosis, neuroinflammation, and glymphatic dysfunction.	Animal study: mice	IL-1 β , TNF- α , GFAP, Iba1, A β , microglial and astrocyte counts	<i>P. gingivalis</i> caused gut dysbiosis, immune cell infiltration, reduced glymphatic clearance, neuroinflammation, and A β accumulation.	Provides evidence that periodontal pathogens impact the gut-brain axis, leading to neuroinflammation and cognitive dysfunction.
Tang et al. (2021) (41)	Investigate the effects of <i>P. gingivalis</i> on tau hyperphosphorylation and neuroinflammation in rats.	Animal study: rats	Phosphorylated tau (Thr181, Thr231), IL-1 β , IL-6, TNF- α , Protein phosphatase 2A (PP2A).	<i>P. gingivalis</i> infection led to tau hyperphosphorylation, elevated neuroinflammatory cytokines, and PP2A inhibition.	Direct evidence of <i>P. gingivalis</i> contributing to neuroinflammation and tau pathology in AD.
Bahar et al. (2021) (42)	Investigate the effects of oral <i>P. gingivalis</i> (W83) infection on AD pathophysiology	Animal study: mice	A β , NFTs, IL-1 β , IL-6, TNF- α , oxidative stress markers.	<i>P. gingivalis</i> infected mice exhibited neuroinflammation, tau	Demonstrates a mechanistic link between <i>P. gingivalis</i> infection,

	y in obese, diabetic mice.			phosphorylation , and upregulation of insulin resistance-related genes.	systemic inflammation, and neurodegeneration.
Qiu et al. (2021) (43)	Compare inflammatory responses triggered by lipopolysaccharide (LPS) from Porphyromonas gingivalis vs. Escherichia coli in microglial cells.	In vitro study	IL-1 β , IL-6, TNF- α , IL-17, IL-23, TLR2/4, NF-kB/STAT3.	<i>P. gingivalis</i> LPS induced a weaker inflammatory response compared to E. coli LPS, affecting NF-kB/STAT3 activation differently.	Explores mechanistic differences in neuroinflammation triggered by periodontal pathogens.
Zeng et al. (2021) (44)	Investigate Cofilin 2 as a molecular link between chronic periodontitis and AD.	Animal study: mice	Cofilin 2, PP2A, Tau phosphorylation , <i>P. gingivalis</i> lipopolysaccharide (LPS), TGF- β 1.	Chronic periodontitis increased Cofilin 2 levels, promoting tau hyperphosphorylation via inflammation; TGF- β 1 upregulated Cofilin 2.	Identifies a molecular link (Cofilin 2) between periodontitis and AD via neuroinflammation.
Tran et al. (2021) (45)	Examine how <i>P. gingivalis</i> causes neuroinflammation and neurodegeneration in a human neural cell model.	In vitro study	NO, pTau, CD86, iNOS, IL-1 β , TNF- α , IL-6.	<i>P. gingivalis</i> metabolites triggered microglial activation, oxidative stress, and neurodegeneration.	Provides direct molecular evidence of neuroinflammation and neurodegeneration induced by periodontal pathogens.
Liu et al. (2020) (46)	Investigate the neuroprotective effects of Salvianolic Acid B (SalB) against <i>P. gingivalis</i> -induced cognitive impairment.	In vivo study	IL-1 β , IL-6, A β 1-40, A β 1-42, ADAM10, BACE1, PS1, LRP1, RAGE.	SalB reduced neuroinflammation and A β accumulation, suggesting therapeutic potential against <i>P. gingivalis</i> -associated cognitive decline.	Shows a potential intervention for <i>P. gingivalis</i> -induced neuroinflammation in AD.

Leira et al. (2020) (47)	Investigate whether periodontitis is associated with amyloid beta (A β) peptide and if systemic inflammation mediates this link.	Human case-control study (n=150)	IL-6, hs-CRP, A β 1-40, A β 1-42.	Patients with periodontitis had elevated IL-6, hs-CRP, and A β levels. Systemic inflammation mediated this association.	Supports systemic inflammation as a mediator between PD and increased A β peptides linked to AD.
Haditsch et al. (2020) (48)	To investigate whether Porphyromonas gingivalis can invade neurons and cause neuroinflammation and Alzheimer's-like pathology in vitro.	In vitro study	Autophagic vacuoles, Multivesicular bodies, Phosphorylated tau (pTau at T231), Synaptic density reduction.	<i>P. gingivalis</i> invaded neurons, leading to accumulation of autophagic vacuoles, tau phosphorylation, and synaptic loss, resembling Alzheimer's pathology.	Provides direct evidence that <i>P. gingivalis</i> infects neurons, triggering neuroinflammation and tau pathology similar to Alzheimer's.
Díaz-Zúñiga et al. (2020) (49)	To evaluate whether different serotypes of <i>P. gingivalis</i> trigger neuroinflammation and AD markers in wild-type rats.	Animal study: rats	IL-1 β , IL-6, TNF- α , IFN- γ , Astrocyte and microglia activation, Amyloid-beta (A β 42), Tau hyperphosphorylation.	Encapsulated serotypes (K1, K2) of <i>P. gingivalis</i> triggered significant production of inflammatory cytokines and increased A β accumulation.	Shows that specific <i>P. gingivalis</i> serotypes drive cytokine production and Alzheimer's markers in an animal model.

Neuroinflammation and Microglial Activation

The studies by Li et al. (2024), Qiu et al. (2025) and Almarhoumi et al. (2023) all focused on neuroinflammation and microglial activation in the context of PD and AD.

Firstly, neuroinflammation was identified in mice who were orally administered *P. gingivalis* displaying inflammatory cells in their brain tissue (24). Subsequently, when HMC3 human microglial cells were exposed to the bacterium in vitro, M1 polymerization was detected by the increased expression of CD86 and iNOS, upregulation of proinflammatory cytokines (IL-6, IL-17), downregulation of anti-inflammatory cytokine (IL-10) which decreased the viability of microglial in vitro (24). Activation of the NF- κ B signaling pathway in microglia was detected by the increased p-P65 and decreased p-I κ B α (24). When an inhibitor of the NF- κ B signaling

pathway was used called QNZ, there was a decrease in proinflammatory cytokines, reversed M1 polymerization and improved microglial cell viability.

Secondly, intravenous injection of *P. gingivalis* or its OMVs into mice showed significant cognitive deficits and hippocampal neuroinflammation based on astrocytic activation (GFAP), microglial activation (Iba1), IL-1 β , TNF- α , and IL-6 levels (22). Mice injected with the whole *P. gingivalis* showed signs of systemic inflammation while mice injected with the OMVs showed signs of down regulation of tight junction proteins in the blood brain barrier causing localized inflammation(22).

Thirdly, ligature induced PD mice displayed bone loss, inflammation, higher numbers of activated microglia (CD45^{low} CD11b⁺) and higher number of activation markers in the brain (MHCII, CX3CR1, CD68) (34). Microglial cells stimulated with *K. variicola* showed significant increase in IL-1 β , IL-6, TNF- α and upregulation of TLR2, TLR9 (34). Microglial cell exposure to PD microbiome and *K. variicola* increased microglial phagocytosis of amyloid-beta (A β 42) caused by a 33-fold increase in MSR1 (macrophage scavenger receptor 1) levels but when TLR2 or TLR9 were inhibited, reduction of MSR1 expression led to significant reduction of A β 42 uptake.

P. gingivalis role in Tau Hyperphosphorylation and Amyloid-Beta Pathology

The studies by Tang et al. (2021), Ciccotosto et al. (2024) and Verma et al. (2023) all focused on effects and mechanisms of *P. gingivalis* in causing AD pathologies such as tau phosphorylation and A β plaque formation due to PD. All three studies showed that *P.gingivalis* has the capacity to cause these pathologies through different but overlapping processes.

Firstly, rats that were repeatedly injected with *P. gingivalis* displayed a significant amount of tau hyperphosphorylation at distinct AD-related sites in the hippocampus (pTau181 and pTau231), activation of astrocytes and increased levels of IL-1 β , IL-6, TNF- α (41). A suppression of the protein phosphatase 2A (PP2A) which is responsible for tau dephosphorylation was noticed in the infected rat population (41). Alongside in the in vitro study, IL-1 β cytokine alone showed the ability to suppress the activity of PP2A (41).

Secondly, chronic oral inoculation of *P. gingivalis* and *T. denticola* in a mouse model displayed wide pathologies (25). *P. gingivalis* alone induced A β plaque accumulation, tau phosphorylation, neuronal loss, increase in IL-1 β , IL-6, astrocyte and microglial activation (25). While *T. denticola* alone only caused neuroinflammation and neuronal damage without tau or amyloid pathologies and inoculation with both bacteria presented milder brain pathologies compared to *P. gingivalis* alone (25).

Thirdly, the effect of *P. gingivalis*-LPS on SH-SY5Y neuroblastoma cells led to increased levels of IL-1 β , IL-6, TNF- α , expression of AD markers (A β 1–42), total tau expression, and increased oxidative stress via TLR4 signaling (29). This was further supported by elevated levels of reactive oxygen species (ROS), reduced mitochondrial membrane potential, and impaired ATP production causing mitochondrial dysfunction (29). When TLR4 was inhibited with CLI-095 many of the pathogenic effects were reversed (29).

Blood-Brain Barrier and Endothelial Dysfunction

The studies by Charoensaensul et al. (2021) and Karakaya et al. (2022) both focused on how *P. gingivalis* impairs the integrity and function of the brain's vascular barrier by targeting endothelial cells.

Live *P. gingivalis* showed the capacity to invade brain endothelial cells causing significant morphological changes, apoptosis, and cell death, yet this was not observed with heat-killed bacteria (50). *P. gingivalis* infection drastically increased intracellular reactive oxygen species (ROS), activated the NF- κ B signaling pathway, and increased levels of IL-1 β and TNF- α causing endothelial cell apoptosis and dysfunction (50). When the antioxidant N-acetylcysteine (NAC) was used there was a significant reduction in ROS levels, NF- κ B activity, cytokine expression, and cell death (50).

Additionally, *P. gingivalis* infection of human brain microvascular endothelial cells (BMVECs) significantly increased the secretion of endothelin-1 (ET-1) which is a powerful vasoconstrictor and upregulated its receptor ETA (39). At the same time, expression of critical tight junction proteins like claudin-5 and occludin were reduced which indicated weakened endothelial barrier function (39). While *P. gingivalis* also induced signs of early cellular senescence, including reduced Lamin A/C and β -galactosidase activity, blocking ET receptors did not prevent these effects (39).

Gut-Brain Axis and Microbiota

The studies by Troci et al. (2024), Chi et al. (2021) and Zhao et al. (2023) all focused on the gut-brain axis and microbiota in the context of AD. All three studies explore a pathological link between gut and oral microbiota and Alzheimer's disease via the gut-brain axis.

Firstly, a microbial analysis was performed in individuals in populations with AD, mild cognitive impairment (MCI), genetically predisposed (APOE4+), and healthy controls

(26). There were correlations in the AD and MCI populations between elevated oral bacteria strains such as *Porphyromonas*, *Haemophilus*, *Neisseria*, and *Actinobacillus* and fecal samples containing elevated proinflammatory strains such as *Bacteroidetes* and *Sutterella* (26). These microbial changes aligned with elevated tau and reduced A β 42 levels (26).

Secondly, mice with orally administered *P. gingivalis* displayed a modified gut microbiota profile containing less beneficial species such as *Parabacteroides gordonii*, *Ruminococcus callidus* and increased harmful species such as *Mucispirillum schaedleri* (40). The infected mice displayed significant cognitive impairment, gut microbiota disruption, and neuroinflammation (40).

Thirdly, the findings showed an alteration in brain microbiota in PD-induced mice populations. The results showed colonization in the brain by PD pathogens and increased levels of IL-1 β , IL-6, TNF- α , A β 42, and phosphorylated tau (32). When these populations were treated with a probiotic bacteriocin nisin, there was a positive change in brain microbiome, decreased levels of neuroinflammatory cytokines and decreased accumulation of pathological proteins (32).

5. DISCUSSION

This review combines findings across the four observed pathways that examines the link between PD pathogens and neuroinflammation in AD. Four main pathways were created to analyze and understand the outcomes of the chosen articles in each category. The discussion section will follow the same format as the results section examining the significance of the results found within these pathways: neuroinflammation and microglial activation, tau hyperphosphorylation and amyloid-beta pathology, blood–brain barrier (BBB) and endothelial dysfunction, and gut–brain axis disruption.

Neuroinflammation and Microglial Activation

The studies by Li et al. (2024), Qiu et al. (2025), and Almarhoumi et al. (2023) illustrate how *P. gingivalis* and other periodontal pathogens can initiate neuroinflammation by activating microglia and shifting them toward a pro-inflammatory (M1) phenotype. This observation is highly important because other studies have also shown that M1 microglia release proinflammatory cytokines like IL-6, TNF- α , and IL-1 β , which not only sustain neuroinflammation but also can cause neuronal damage and synaptic loss which are both hallmark pathologies of AD (51).

The results in the Li et al. (2024) demonstrated that NF- κ B signaling plays a pivotal role in this polarization process by showing that inhibitor QNZ is able to reverse M1 polarization and restore microglial viability. This provides good evidence which is also supported in other studies that show that NF- κ B is a central inflammatory agent in PD-related brain pathology (52). This is

significant because when the NF- κ B pathway is upregulated in AD brains, it has been linked to both tau phosphorylation and amyloidogenesis (53). Therefore, identifying this pathway can create a therapeutic target for future therapies.

The outcome of the Qiu et al. (2025) gave additional information about the pathogenesis of *P. gingivalis* by comparing the systemic effects of *P. gingivalis* versus its outer membrane vesicles (OMVs). The systemic immune activation seen in Pg-injected mice, specifically of the NLRP3 inflammasome pathways highlights the grand capacity of this bacterium. Another study has also reported that the NLRP3 inflammasome pathway is activated in cells from patients with severe chronic periodontitis (54). Alternatively, OMVs compromise the BBB directly which leads to localized CNS inflammation. These findings are particularly important because they show that even partial bacterial components such as the OMVs have the capacity to cause neuroinflammation. This data is supported by another study that reported *P. gingivalis*-OMVs impaired memory, activated astrocyte and microglia (55).

Almarhoumi et al. (2023) reported an important finding that shows *Klebsiella variicola* to upregulate microglial activation and amyloid-beta phagocytosis. The reported upregulation that led to the elevated MSR1 expression and a dramatic 33-fold increase in A β 42 uptake by microglia causes excessive and dysfunctional phagocytic activity leading to neuroinflammation and neuronal stress. These results emphasize that although A β 42 uptake by microglia is necessary for protection, data from another study also conclude that persistent activation and excessive uptake of A β 42 causes neuroinflammation (56). These results support the idea that chronic PD creates a primed, pro-inflammatory microglial environment favorable to neurodegeneration.

Tau Hyperphosphorylation and Amyloid-Beta Pathology

Tau hyperphosphorylation and amyloid-beta deposition are key pathological hallmarks of AD. The studies by Tang et al. (2021), Ciccotosto et al. (2024), and Verma et al. (2023) reveal how *P. gingivalis* and its virulence factors induce or exacerbate Tau hyperphosphorylation and amyloid-beta deposition through inflammatory and mitochondrial mechanisms.

Tang et al. (2021) found that *P. gingivalis* elevates pro-inflammatory cytokines and significantly suppressed PP2A activity which is an enzyme responsible for dephosphorylating tau. The inhibition of PP2A by IL-1 β alone in vitro displays a direct cytokine-mediated pathway for tau pathology. Previous studies have reported PP2A and IL-1 β to be dependents in other regulatory processes that are part of pro-inflammatory feedback loops (57).

The results from Ciccotosto et al. (2024) suggest a specificity in pathological potential of *P. gingivalis* including known virulence factors such as gingipains, LPS and OMVs seen in the previously discussed studies. These virulence factors have been shown to cause and exacerbate AD-like neuropathologies. Interestingly, co-inoculation with *T. denticola* diminished these effects, possibly due microbial interference or competition. These results go against the results of the previous study where inoculation with *P. gingivalis* and *T. denticola* showed synergistic pathological effects in host immune response and alveolar bone loss in mice (58).

The outcome of Verma et al. (2023) study shows how Pg-LPS induces oxidative stress, disrupts mitochondrial function, and activation of TLR4-dependent inflammatory cascades contributes to increased expression of A β and tau. The solidifying outcome of this study showed that TLR4 inhibition reversed these effects creating this as a possible therapeutic target for future therapies in preventing or pausing AD-related pathologies. Other studies have reported the same relationship between TLR4 inhibition and reduction in neuroinflammation and neuronal damage (59).

Added together, these studies highlight the role of *P. gingivalis*-induced inflammation as a trigger for tau pathology and amyloidogenesis.

Blood–Brain Barrier and Endothelial Dysfunction

BBB disruption is an early event in AD, and studies by Charoensaensuk et al. (2021) and Karakaya et al. (2022) reveal how *P. gingivalis* compromises this critical barrier. Previous works have shown evidence on the bacterial invasion of the brain and have identified other bacteria such as *C. pneumoniae*, *B. burgorferi*, *H. pylori*, *C. acnes*, and some strains of Fungi (60).

The finding in Charoensaensuk et al. (2021) showed that only live *P. gingivalis* could invade endothelial cells as opposed to heat-killed controls which leads us to believe that there is importance of bacterial metabolism. A previous study has shown that gingipains are a necessary virulence factor to cause epithelial cell apoptosis which may help explain the reason why only live *P. gingivalis* were able to invade endothelial cells(61).

Karakaya et al. (2022) outcome highlighted an important pathway that was caused by *P. gingivalis* increasing ET-1 and ETA receptor expression, resulting in vasoconstrictive signaling, and reduced expression of tight junction proteins like claudin-5 and occludin. These results display rarely described pathogenic effects of *P. gingivalis* causing not only inflammatory but also structural impairment of endothelial cells. Due to the recency and specificity of this research only studies regarding expression of tight junction protein in epithelial cells showed similar patterns suggesting that *P. gingivalis* can affect expression of tight junction proteins (62).

These results emphasize that *P. gingivalis* disrupts the BBB both functionally and physically, creating a pathway for the entry of inflammatory cells and microbial components into the brain causing neuroinflammation and AD pathologies.

Gut–Brain Axis and Microbiota

The studies by Troci et al. (2024), Chi et al. (2021), and Zhao et al. (2023) all highlight the role of oral and gut microbiota dysbiosis in affecting brain health. This newly developing pathway has the potential to link PD-induced gut microbiota dysbiosis to affecting cognitive function. Troci et al. (2024) showed microbial shifts in AD and MCI patients have correlation with pathological CSF biomarkers (reduced A β 42, elevated pTau), which both are AD pathologies implying that microbiota may influence AD onset and progression. A previous study had a similar correlation between mice who were administered *P.gingivalis* versus a control group showing a significant

difference in gut microbiota and additionally reported a disruption in the gut barrier function (63).

Chi et al. (2021) provided mechanistic insight by showing that *P. gingivalis* administration in mice led to loss of beneficial gut microbes and an increase of inflammatory strains. These changes were positively correlated with increased brain infiltration of immune cells, glymphatic system dysfunction, and most importantly amyloid accumulation. These changes demonstrate a positive link between gut dysbiosis and central nervous system pathology. Previous studies have also shown to have bidirectional communication between organs and the CNS (64). The noticed decline in gut microbiota which is responsible for producing anti-inflammatory metabolites can be viewed as a loss of immune regulation due to the *P. gingivalis* infection.

The demonstrated success of the probiotic nisin in the Zhao et al. (2023) study showed its ability to reverse many of these AD-related pathologies. This result shows that nisin has the therapeutic potential in restoring microbiota balance and has protective qualities for the brain. By changing the brain microbiome, reducing inflammatory cytokines, and lowering A β and tau levels, nisin demonstrates a pivotal example of a targeted therapy. Another study has been performed to review the success probiotic therapies showed mixed results. There were initial improvements in the severe cases but showed a decline over time which also highlighted a potential restriction due to the need for further research on optimal strains, dosages, and long-term efficacy (65). Continued research of therapies like this which are non-invasive but have the capacity to be added to other preventative strategies of neurodegenerative diseases. Together, these studies highlight the gut–brain axis as a two-way pathway through which PD-induced dysbiosis can influence cognitive function.

6. CONCLUSION

In conclusion, the literature review of 28 articles reinforced possible pathways PD pathogens contribute to neuroinflammation in AD. The examination of the articles provided four possible pathways neuroinflammation was caused by PD pathogens. Studying and further researching these pathways brings light to possible treatment targets.

This research reveals that PD is greatly intertwined with many systemic mechanisms, showing evidence of having the ability to accelerate progression of AD. This insight demands a fundamental rethink of PD's role within the human body. It should no longer be thought of as a disease affecting the oral cavity, but a critical element in brain health and a modifiable risk factor in the fight against AD.

For the future, this review illuminates exciting areas for discovery. The path ahead demands further studies to reveal greater mechanisms of both diseases which can bridge these conditions and unlock more insights. This can bring to the development of targeted treatments helping future generations decrease the rising number of patients with PD and AD. This evidence can push people's perspective that oral health is an important factor in health care.

7. SUSTAINABILITY

Maintaining oral health is not only essential for individual well-being but also for reducing the systemic burden of chronic diseases such as Alzheimer's, thereby lowering long-term healthcare demands, costs and all other equipment benefiting the environment. By addressing periodontal disease early, we can mitigate neuroinflammation, promote cognitive longevity, and support healthier aging populations. This interdisciplinary approach underscores the role of preventive dental care in advancing sustainable public health outcomes.

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