FROM ORAL HYGIENE TO COGNITIVE HEALTH: EXAMINING THE RELATIONSHIP BETWEEN PERIODONTAL DISEASE AND ALZHEIMER'S

ABSTRACT

Aim: The aim of this study was to review the literature in an integrative way, looking for scientific evidence to see if there is a relationship between periodontal disease (PD) and Alzheimer's disease (AD).
Study design: Review the literature in an integrative.
Methodology: The search was carried out on the VHL Regional Portal with articles published in English, Spanish and Portuguese. 169 articles were found between 2021 and 2023. Of this total, 106 were excluded, 5 for being duplicates and 101 for not meeting the inclusion criteria. Of the studies analyzed, most report evidence of an association between PD and AD, with *Phorphyromonasgingivalis* (PG) as the common pathogen in both conditions.
Results: The results revealed four aspects: a) PG and other periodontopathogens (PP) play a role in the systemic inflammation process that accelerates the onset and progression of AD; b) even given the link between the oral-brain aetiological axis hypothesis of a brain degeneration syndrome such as AD, it is still necessary to further investigate the role of PP and PG (multimicrobial hypothesis) in the pathogenesis and worsening of AD; c) PD represents a factor in the progression of AD via induced pathogenic bacteria, since these individuals may have poor oral hygiene care, due to forgetfulness or less manual dexterity; d) Age and gender are important variables to consider when assessing the association between PD and AD.
Conclusion: Thus, we can infer that despite the number of studies observed through this integrative review, there is still not enough research with a high level of scientific evidence on this association. Thus, new studies with greater methodological rigor in terms of the methods applied and the criteria for diagnosing the pathologies need to be carried out in order to obtain a better understanding of the relationship between PD and AD.

Keywords: Periodontal disease. Alzheimer's Disease. Periodontitis.

1. INTRODUCTION

Alzheimer's disease (AD) is a degenerative disease that causes neuron atrophy, leading to a reduction in mental function, especially in elderly patients, which in turn leads to memory loss and a lack of mental abilities [1,2].

"A characteristic symptom of AD is the progressive shrinking of the hippocampus, which is responsible for storing long-term memories, spatial processing and navigation. More than 55 million people live with dementia

worldwide; AD represents 60% to 70% of cases" [3]."The exact cause of AD remains elusive; only a small fraction, around 1-2%, of AD cases are directly inherited and follow an autosomal dominant pattern. This form, known as familial AD, has early onset symptoms and a rapid progression of symptoms. Early onset AD is commonly attributed to genetic factors, suggesting a strong hereditary component. On the other hand, sporadic or late-onset AD, which accounts for the majority of cases, is believed to result from a complex interaction between genetics and environmental factors. It is important to note that while early onset AD tends to have a stronger genetic basis, late onset AD is a multifactorial condition influenced by a combination of genetic susceptibility and environmental factors. This intricate interaction underscores the complexity of understanding and addressing the various risk factors associated with Alzheimer's disease" [4].

"Periodontitis is a chronic immunoinflammatory disease of the soft and hard tissues caused by the interaction of the microbial biofilm formed around the teeth with the host [5]. *Porphyromonasgingivalis,* a Gram-negative anaerobic bacterium, is highly invasive of gingival epithelial tissues and has been identified as one of the main pathogens causing periodontitis, which in turn can reach other organs in the body, such as the brain"[6,7].

"In addition, periodontal disease is currently one of the six most common inflammatory diseases worldwide, with a high risk of causing complications of other inflammatory diseases such as diabetes, cardiovascular disease and Alzheimer's disease"[8]. "Thus, understanding the etiology of periodontitis is a challenge given its multicausal nature involving complex and dynamic interactions between the host immune system, microbiome, genomics, lifestyle and environmental factors"[9].

In this sense, some studies [10,11,12,13,14] suggest that the occurrence of *P. gingivalis* in periodontal tissues may be a risk factor for the aggravation of degenerative diseases such as Alzheimer's disease, causing even greater cognitive impairment in these individuals. However, there is another view that periodontal disease may be related to the onset or emergence of Alzheimer's disease. In view of this, four guiding questions emerge from this research: a) Is there an association between Alzheimer's disease and periodontal disease? b) Can periodontal disease be involved in the cause of Alzheimer's disease or can Alzheimer's disease cause or aggravate periodontal disease? c) Is periodontal disease an etiological risk factor (development) or a modulator (modifier) of Alzheimer's disease? d) Can age and gender influence the correlation between periodontal disease and Alzheimer's disease?

This research intends to gather scientific evidence from recently published studies that can clarify the guiding questions presented here. Studies have been identified showing results with two types of association, directional and bidirectional. Hence, it is considered important to discuss the topic by filling these gaps.

Therefore, the aim of this study was to conduct an integrative review of the current literature to analyze if there is a relationship or association between periodontal disease and Alzheimer's disease.

2. METHODOLOGY

This is an integrative literature review on the possible relationship or association between periodontitis and Alzheimer's disease. The online bibliographic survey was carried out through the VHL (Virtual Health Library) Regional Portal (https://pesquisa.bvsalud.org/), a free-access electronic database.

The choice of this research method or strategy for this literature review was based on the understanding of Botelho et al. (2011) and other authors [15,16], aiming to synthesize the findings of several selected studies of different methodologies already published, making an analysis of the knowledge already built on a specific topic, using a rigorous method of search and selection of research.The objectives of this review include reviewing theories,

analyzing methodological problems in a given topic, defining concepts and, finally, finding evidence. At the same time, the aim of this review is to search for evidence on the relationship or association between periodontal disease and Alzheimer's disease.

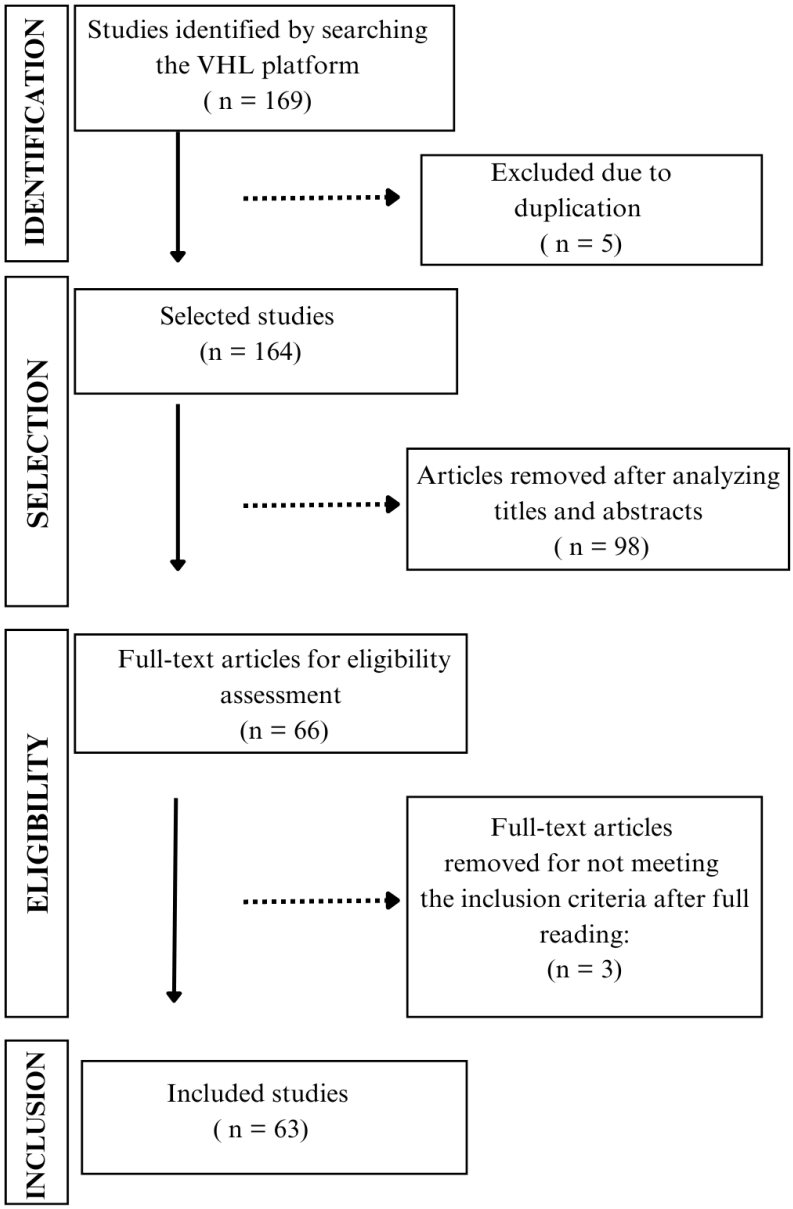
The following keywords were used: "periodontitis", "periodontal" and "alzheimer". The advanced search strategy was carried out using the following descriptors: "periodontitis" OR "periodontal" AND "alzheimer". These terms could be in the title, abstract or main subject of different articles.

Firstly, the studies were selected by title, excluding those that were clearly not related to the theme of the review. Only recent articles that addressed the relationship or association between periodontitis or periodontal disease and Alzheimer's disease were used as inclusion criteria for this research,in both humans and animals, with texts written in English, Spanish and Portuguese. Excluded from this review were opinion articles that did not clearly report the relationship or association between periodontitis or periodontal disease and Alzheimer's disease, but also research that was not available to read in full in open access.

Once the search engine had been used and the articles identified, the studies were selected according to the guiding questions and inclusion criteria already defined. All the studies identified through the search strategy were initially assessed by analyzing the titles and abstracts.In cases where the titles and abstracts were not sufficient to define the initial selection analysis, the study was then read in its entirety.

“With this in mind, the integrative review process followed a succession of stages, consisting of six phases: (1) identification of the topic and selection of the research question; (2) establishment of inclusion and exclusion criteria; (3) identification of the pre-selected and selected studies; (4) categorization of the selected studies; (5) analysis and interpretation of the results; and (6) presentation of the review/synthesis of knowledge”[17]. Figure 1 graphically shows an overview of the integrative review selection process.

Figure 1 - Flowchart of the methodological steps.



Source: Prepared by the authors (2024).

3. RESULTS

This section contains the main results of the studies selected in this integrative review, according to the synthesis matrix (Table 1). As previously described, 169 articles were identified in this search carried out in the VHL Regional Portal database. Of this total, five duplicates were excluded, leaving 164. After analyzing the titles and abstracts, 98 were also excluded as they did not meet the inclusion criteria. Therefore, 66 were subjected to eligibility assessment by reading the studies in full and3 of the studies were removed. Thus, a total of 63 studies were included. (Figure 1).

Table 1 - Synthesis matrix used in this integrative review.

N	Authors/Year	Objective	Methodology	Main findings
[18]	Araújo et al. (2021)	To test the hypothesis that periodontitis is associated with Alzheimer's disease (AD) and to investigate whether periodontal and other variables have a negative impact on the perception of oral health-related quality of life.	Descriptive and observational study	Periodontitis was associated with AD, but not with patients' oral health.
[19]	Bahar et al. (2021)	To investigate the effect of oral infection by *P. gingivalis* (W83) on the development of the pathophysiology of Alzheimer's disease in a wild-type obese and diabetic mouse model.	Experimental study carried out on obese and diabetic mice	PG (W83) infection of ob/db mice provided a comorbidity model with the potential to reproduce the pathophysiology of AD with induced periodontal disease.
[20]	Beydoun et al. (2021)	To analyze whether co-infection between *Helicobacter pylori* (Hp) and groups of periodontal pathogens can alter the onset of Alzheimer's disease and dementia.	Experimental study carried out with 1,431 individuals over 65 years of age	It was found that *Prevotella intermedia, Campylobacter Rectus*, Factor 2 (Pi/*Prevotellanigrescens/Prevotellamelaninogenica*) and the cluster orange-red cluster interacted synergistically with Hpseropositivity, particularly with regard to the incidence of AD.
[21]	Chi et al. (2021)	To investigate whether *P. gingivalis* (PG) induces cognitive impairment by disturbing the gut-brain axis.	Experimental study	The findings indicated that PG may play an important role in intestinal dysbiosis, neuroinflammation and impairment of the lymphatic system, which in turn may lead to cognitive impairment.
[22]	Guo et al. (2021)	To analyze the characteristics of oral microbiomes and hoping to find biomarkers for Alzheimer's disease.	Experimental study	The microbiome community of oral microbes was altered in patients with Alzheimer's disease and the periodontal microbiome was sensitive to changes in cognition. In addition, *Veillonellaparvula*and *P. gingivalis*were associated with AD.
[23]	Kamer et al. (2021)	To test the hypothesis that in cognitively normal elderly people, dysbiosis of the oral subgingival microbiome is associated with cerebrospinal fluid (CSF) evidence of AD pathology, which includes Aβ and	Cross-sectional and descriptive study	At gender and species levels, greater subgingival periodontal dysbiosis was associated with reduced amyloid beta (Aß)42 in the CSF, but not with Tau protein. The results showed that dysbiotic periodontal bacteria are associated with

		tauopathy.		biomarkers of amyloidosis in CSF, but not neurofibrillary pathology, leading to the hypothesis that periodontal dysbiotic effects on AD pathology are an early event
[24]	Laugisch et al. (2021)	To compare periodontal and dental status in patients with AD or other forms of dementia.	A descriptive and observational study.	Both patients with AD and other forms of dementia had periodontal disease. Thus, patients with all forms of dementia (AD/other) need special dental care to improve periodontal and oral health.
[25]	Patel et al. (2021)	To characterize the human genes modulated by *P. gingivalis*.	Experimental study	The results suggest markers of neural infection by PG and link the cholinergic and gingipain hypotheses in the development of AD.
[26]	Qian et al. (2021)	To investigate the effect of periodontitis on the learning and memory capacity of amyloid-ß protein (AßPP)/presenilin (PS1) precursor transgenic mice, together with the mechanisms underlying these effects.	Experimental study carried out on mice to induce periodontitis	Data indicated that periodontitis exacerbated learning and memory impairment in AßPP/PS1 mice and increased Aß and neuroinflammatory responses. This study provides a theoretical basis for risk prediction and early intervention in Alzheimer's disease and periodontitis.
[27]	Aravindraja et al. (2022)	To evaluate the effects of oral bacterial infection by periodontal bacteria bacteria (*P. gingivalis, Treponemadenticola*) and supragingival commensals (*Streptococcus gordonii*) on APP transgenic CRND8.	Experimental study	Intracerebral *P. gingivalis* infection exacerbated significant Aβ deposition, amyloid load and induces microgliosis in APP transgenic mouse models.
[28]	Lu et al. (2022)	To investigate the impact of periodontitis-related salivary microbiota on AD by gavaging salivary microbiota from periodontitis and healthy subjects in an APP swe/PS1 ΔE9 (PAP) mouse model of AD.	Experimental study	The data reinforced the role of periodontitis-related salivary microbiota in the interference between the intestine and the brain during the progression of AD.

[29]	Sansores-Espanha et al. (2022)	To determine periodontal status, pro-inflammatory mediators, PG load and Apolipoprotein E (ApoE) in AD patients.	Experimental study	The pro-inflammatory mediators and the PG load had a negative correlation with the test scores. In AD patients, we found more severe periodontitis, higher levels of pro-inflammatory mediators and a higher bacterial load. In addition, an increase in ApoE makes it possible to clearly determine patients with health, periodontitis and periodontitis and AD.
[30]	Wu et al.(2022)	To explore the impact of *F. nucleatum* on AD progression in *in vitro* experiments and in animal models, providing initial evidence of the possible association between a periodontal pathogen and AD and an understanding of the underlying mechanisms.	Experimental study	*F. nucleatum* activates microglial cells *in vitro*, promoting proliferation and increasing the inflammatory response. *In vivo*, in a rat model of periodontitis, *F. nucleatum* accelerates the development of the disease by promoting inflammatory responses in the brain, exacerbating the behavioral and pathological manifestations of rats. As a periodontal pathogen, *F. nucleatum* accelerates the development of AD.
[13]	Schwahn et al. (2022)	To investigate the relationship between periodontal treatment and preclinical AD.	Experimental study	Data indicated that periodontal treatment had a favorable effect on decreasing AD-related brain atrophy. However, for brain aging, the effect of treatment was uncertain.
[31]	Chen et al. (2023)	To investigate gender and age differences in the characterization of periodontal bone tissue, immune status and cognitive function in a murine model of Alzheimer's disease amyloid precursor protein/presenilin 1 (APP/PS1)	Experimental study	The data emphasized that age and gender are important variables to consider when evaluating the periodontal bone tissue of APP/PS1 mice, and cognitive impairment is more closely related to age.
[32]	Fu et al. (2023)	To investigate the association between Alzheimer's disease and periodontitis in terms of periodontal status, serological markers and oral microbiome.	Experimental study	Alzheimer's disease patients with a Clinical Dementia Rating (CDR) ≥1 exhibited significantly more clinical attachment loss (CAL) than those with a lower CDR. Serum levels of Tau protein, hsCRP and anti-*P. gingivalis* LPS antibody were markedly elevated in the AD group compared to the control group. The serum level of pTau protein was positively correlated with the titer of anti-*P. gingivalis* LPS antibodies. The study

				suggested the association of periodontal infection and oral microbiome with AD.
[33]	Matsumoto et al.(2023)	To elucidate the relevance of oral conditions and β-amyloid (Aβ) and tau pathologies in human participants	Experimental study	Findings with previous preclinical evidence imply that tooth loss may enhance the pathogenesis of AD tau by promoting the spread of tau from the LC to the hippocampus formation.
[34]	Saji et al. (2023)	To evaluate associations between PD and neuropsychological test sub-items.	It was made a cross-sectional analysis of data from (n = 183) participants (women: 50%, mean age: 79 years) in a clinical study.	Participants with dementia were less likely to make regular visits to the dentist, had fewer teeth, had less frequent tooth brushing habits and were more likely to have PD. Impaired cognitive function was significantly associated with an increasing degree of PD.
[35]	Wang et al. (2023)	To delineate the role of cytokines in the pathogenesis of periodontal disease and Alzheimer's disease.	Experimental study	The systemic inflammation resulting from periodontitis contributed to the development of the tau pathology of AD and subsequently led to cognitive decline in non-transgenic mice. It also potentiated the pathological features of AD and exacerbated the impairment of cognitive function in mice.
[36]	Wereszczynski et al. (2023)	To investigate the relationship between mind wandering and periodontitis and address the lack of a deeper understanding of the relationship between oral health and cognitive abilities by investigating whether periodontitis is primarily associated with memory.	Experimental study	A worsening of periodontal health was associated with worse episodic memory, with no relationship between periodontitis and the measure aimed at various cognitive abilities, from which memory was excluded.
[37]	Yang et al. (2023)	To examine the periodontal condition of patients with AD and to track salivary metabolic biomarkers in the saliva of individuals with and without AD with compatible periodontal conditions.	Experimental study	Dysregulation of the proportion of specific bacterial flora in saliva plays a vital role in the metabolic changes in AD. These results may contribute to further improving the salivary biomarker system for AD.

[38]	Dewey e Rishniw (2021)	To compare visual periodontal scores (from digital oral photographs) with numerical (0-54) cognitive assessment forms in elderly dogs with and without a clinical diagnosis of canine cognitive dysfunction.	Prospective case-control study	Although a cause-and-effect relationship between periodontal disease and cognitive impairment can't be determined from this preliminary study, a link between these two disorders has been established that warrants further investigation using more rigorous criteria to assess periodontal disease and cognitive cognitive dysfunction.
[39]	Ma et al. (2022)	To identify the relationship between the longitudinal risk of developing PD in a cohort of patients with dementia and AD who did not show any signs of PD at the beginning of the study.	Population-based cohort study	The results were persistent for AD patients: the relative risk and adjusted hazard ratio of PD in AD patients were significantly higher than in the non-AD cohort. The results showed that dementia and AD were associated with a higher risk of PD depending on age and independent of other systemic factors.
[40]	Carballo et al. (2023)	To assess whether periodontitis is associated with cognitive decline and its progression, as well as with certain blood markers of Alzheimer's disease.	Secondary analysis using data from a prospective cohort study	Periodontitis is associated with cognitive decline and its progression in elderly patients with a previous history of hypertension. Overexpression of p-Tau and Aβ 1-40 may play a role in this association.
[41]	Karaduran et al. (2023)	To investigate the effect of periodontitis and the current occlusal relationship on the rate of progression of Alzheimer's disease.	Cohort study	Within the limits of the study, it can be concluded that periodontitis can increase the severity and also accelerate the rate of progression of AD.
[42]	Borsa et al. (2021)	To examine the link between Alzheimer's disease and periodontal disease (PD) in patients aged 65 and over.	Systematic review	In fact, patients with AD appear to have a lower level of oral hygiene and a higher risk of PD. In this context, periodontopathogenic bacteria have been found in these patients, associated with a higher risk of incidence or mortality, or inversely associated with these risks.
[43]	Costa et al. (2021)	To analyze whether animals infected with PG or bacterial lipopolysaccharide (PG-LPS) are more affected by neurodegeneration, similar to the pathogenesis generated by Alzheimer's disease, compared to non-infected animals.	Systematic review article composed of *in vivo* preclinical studies in mice that were infected with PG or received PG-LPS	PG infection and PG-LPS administration seem to be related to the pathogenesis of AD by activating the complement cascade, increasing Aβ production and increasing the expression of pro-inflammatory cytokines, causing age-dependent brain inflammation, neuroinflammation and neurodegeneration.

[44]	Elwishahy et al.(2021)	To verify the association between *P. gingivalis* and Alzheimer's disease, as well as to identify the homogeneity of the methods used among the studies to measure the involvement of PG in AD.	Systematic review	The included studies suggested that PG plays a role in the process of systemic inflammation that leads to inflammation of the cerebrospinal fluid and indirectly causes acceleration of the onset and progression of AD.
[45]	Hu et al. (2021)	Systematically evaluate the correlation between PD and the risk of AD or MCI.	Systematic review and meta-analysis	This meta-analysis indicated that PD was related to a high risk of AD and cognitive impairment, and should receive early intervention.
[46]	Lorenzi et al. (2021)	To establish the role of *P. gingivalis* in Alzheimer's disease in animals and humans.	Systematic review	An inflammatory condition in the oral cavity may be linked to a brain degeneration syndrome, such as dementia and AD. However, a strict connection has not yet been established. Further studies are recommended to investigate the role of periodontal bacteria such as PG in the pathogenesis and worsening of AD.
[47]	Parra Torres et al. (2021)	To analyze evidence that combines the detection of oral bacteria in the brain, both in animals and in humans affected by Alzheimer's disease	Systematic review	There is evidence of a microbiological susceptibility to developing AD when most of the oral bacteria associated with dysbiosis are present. The presence of bacteria in the brain is related to the pathological characteristics of AD, suggesting an oral-brain etiological axis.
[48]	Sedghi et al. (2021)	Review the progression of periodontal disease and integrate new research concepts into understanding the involvement of PD in systemic health.	Systematic review	Recent studies have also identified the reciprocal importance of periodontal disease in potentiating systemic disease states at distal sites, such as Alzheimer's disease, inflammatory bowel diseases and oral cancer, further highlighting the importance of the oral cavity in systemic health.
[2]	Werber et al. (2021)	To review the potential link between periodontitis and neurodegeneration	Systematic review	Although the studies analyzed have a wide variety of methodological differences to obtain results focusing on the link between AD and PD, physiology studies have revealed potential mechanisms for periodontal

				bacterial contribution to neurodegeneration. PD is the most common dental disease and shares many modifiable risk factors with AD.
[49]	Hao et al. (2022)	Support the importance of periodontal infection in the innate immune regulation of AD and the possibility of targeting microbial etiology and periodontal treatment to improve the clinical manifestation and prevalence of AD.	Systematic review	A "two-strike" model of worsening AD progression associated with periodontitis is proposed, with accumulation of β amyloid in the brain as the first "hit" and invasion of Pg into the brain as the second "hit" to facilitate microglial overactivation and loss of synapses in AD in the presence of periodontitis.
[50]	Harding et al. (2022)	To evaluate the effect of AD without various pathologies that may act as confounding factors in the conditions that develop due to the human aging process.	Systematic review	Although current research indicates a potential dependency/relationship between periodontal disease and dementia associated with AD, more research is needed to clarify the directionality of this association.
[51]	Jungbauer et al. (2022)	To analyze the causal relationship between periodontal microorganisms and Alzheimer's disease.	Systematic review	In the elderly, and particularly in patients with cognitive impairment, periodontal therapy is extremely important for improving their quality of life. An effect of periodontal therapy on the oral microbiome and the host response related to cognitive parameters is fundamental to understanding the causal relationships with age-dependent morbidities.
[52]	Kaliamoorthy et al. (2022)	To evaluate the association between periodontitis and Alzheimer's disease based on a systematic review of observational studies carried out over the last decade.	Systematic review and meta-analysis	An affirmative association between PD and AD was obtained from evidence from standard observational studies conducted over the last decade. Individuals with periodontitis were more likely to develop dementia/cognitive loss related to Alzheimer's disease than those without periodontitis

[53]	Kouki et al. (2022)	To present current knowledge on the association between periodontitis and AD, the mechanism by which periodontal pathogens can cause neuroinflammation and how periodontal pathogens can affect the blood-brain barrier.	Systematic review	Evidence shows that bacteria associated with periodontitis and their virulence factors are capable of damaging the blood-brain barrier and play a role in the onset of pathology similar to that found in AD.
[54]	Mao et al. (2022)	To analyze studies that explored the relationship between the oral microbiome and the development of AD using the next generation sequencing technique.	Systematic review	This review suggests that periodontal infection is associated with AD. The contributing microbiome remains unconfirmed, possibly due to different sites or methods of sampling the microbiome. Additional large-scale studies with periodontal intervention and longitudinal follow-up are needed to clarify the relationship between periodontal disease and AD.
[55]	Bouziane et al (2023)	To evaluate the relationship between periodontal disease and the onset and progression of Alzheimer's disease and to determine whether patients with PD would be at greater risk of developing AD compared to periodontally healthy individuals.	Systematic review	The data indicated that patients with PD have a significantly higher risk of AD compared to individuals with a healthy periodontium. However, the results should be interpreted with caution given the methodological limitations encountered.
[56]	Fu et al. (2023)	To explore whether periodontal infection by *P. gingivalis* is associated with AD and to provide possible mechanisms of association.	Systematic review	PG infection increased the expression of pro-inflammatory cytokines IL-6, IL-1β only in middle-aged mice, but not in young mice. Future studies are needed to clarify the exact pathway and mechanisms of PG and AD infections, and to identify effective treatments.
[57]	Larvin et al. (2023)	To evaluate the factors that impact the association of cognitive disorders in people with periodontal disease.	Systematic review and meta-analysis	Prevalence and risk estimates for cognitive disorders associated with PD may be influenced by gender, PD disease classification and severity. More peer-reviewed evidence that takes these study factors into account is needed to form robust conclusions

[58]	Liu et al. (2023)	To evaluate the association between oral bacteria and AD with clinical evidence	Systematic review	We found a tenfold and sixfold increased risk of AD when there were oral bacteria and PG, respectively, in the brain. Although AD patients exhibited lower alpha diversity of the oral microbiota than healthy controls, the findings of the bacterial communities were inconsistent between the studies.
[59]	Malik et al. (2023)	To explore the conditions of periodontal disease among individuals with and without dementia.	Systematic review	This qualitative analysis showed poor periodontal health and increased inflammatory mediators in the case groups compared to the control groups. Therefore, more quality studies and new interventions are needed to reduce the impact of periodontal health on dementia worldwide.
[9]	Nascimento et al. (2023)	To review the literature to assess confounding factors and their level of heterogeneity in the association between periodontitis and AD. In addition, to examine the reporting and interpretation of data in relation to confounding bias.	Systematic review	Most studies presented a low risk of bias. 50% of the articles did not consider confounding; variation in adjustment approaches was observed. In addition, 62% of the studies did not mention bias and 40% did not discuss any limitations on confounding factors. Given the limitations of the study, caution should be exercised to properly interpret the association between periodontitis and AD.
[60]	Pisani et al (2023)	To explore the modes of neurodegeneration that occur in the locus coeruleus during the natural aging process of trigeminal nerve connections and microbial dysbiosis, and postulate a pathogenetic mechanism due to periodontal damage and/or infection.	Systematic review	The evidence provides vital information about how PD and neurodegenerative diseases can be comorbid. The shared neural pathways, neurotropism of major periodontal pathogens such as PG and *T. denticola*, and the notable neuroinflammatoryeffects of ongoing periodontal injury and the consequences of tooth loss highlight the importance of screening for these diseases and providing treatment and adequate monitoring for these patients

[61]	Salhi et al. (2023)	To gather current understanding of the pathophysiological mechanisms linking periodontitis to AD	Systematic review	Systemic inflammation and brain metastatic infections induced by periodontal pathogens contribute to neuroinflammation, amyloidosis and tau phosphorylation, leading to brain damage and subsequent cognitive impairment.
[62]	Tang et al. (2023)	To analyze recent advances in the pathogenesis of AD, the therapeutic agents available, the relevance of periodontitis to AD and the mechanisms of action.	Systematic review	Although much evidence suggests that periodontitis is involved in the progression of AD, the mechanism of interaction between the two diseases has not yet been clarified, and there is still a need for researchers to carry out in-depth studies and identify new effective treatments, which are of great importance for the early diagnosis and treatment of AD and to slow the progression of the disease.
[14]	Weber et al. (2023)	To discuss the potential contribution of the oral microbiome and oral infectious agents to the etiology of AD, and their link to host inflammatory conditions.	Systematic review	We recommend that future studies aimed at elucidating the association between AD and the oral microbiota include longitudinal study designs and employ multiple, complementary approaches to characterizing oral microbiomes, including shotgun metagenomics.
[63]	Desta et al. (2021)	To explore the possible role of PD in the pathogenesis of AD, as the pathological mechanisms underlying AD are the best studied of all types of dementia	Narrative literature review	The inflammatory reaction induced by oral pathogenic bacteria related to PD, through complex pathways, can exacerbate inflammation in the central nervous system, thus contributing to the severe cyclical progression of AD.
[64]	Dhingra et al. (2021)	To identify eligible studies measuring the association between periodontal disease and Alzheimer's disease or mild cognitive impairment.	Narrative literature review	Within the limitations of the included studies, the authors concluded that periodontal disease is related to an increased risk of Alzheimer's disease and mild cognitive impairment.
[65]	Dibello et al. (2021)	To review the existing evidence on operational definitions of oral fragility and suggest assessment and screening tools for this new construct. As well as describing possible relationships between oral	Narrative literature review	The oral microbiota may influence the risk of AD through circulatory or neural access to the brain and interaction with periodontal disease, often causing tooth loss that is also associated with an increased risk of AD. Therefore, oral

		fragility and oral microbiota.		status may be an important contributor to general health, including Alzheimer's disease and late-onset cognitive disorders.
[66]	Fischer et al. (2021)	Check out the future of periodontal medicine	Narrative literature review	In Alzheimer's disease, evidence indicates that periodontal disease can induce systemic inflammation, disruption of the blood-brain barrier, degeneration and cognitive impairment
[67]	Hamza et al. (2021)	To explore the epidemiological evidence on the oral health of individuals with the neurodegenerative conditions of Alzheimer's disease and dementia	Narrative literature review	Patients with AD have reduced salivary secretions and low buffering capacity. Evidence from current literature postulates that individuals suffering from AD and dementia have special oral health needs. Proper oral health management can therefore significantly improve their oral health and overall quality of life.
[68]	Kapila (2021)	To examine the implications of the involvement of viral pathogens in periodontitis and the systemic implications of periodontitis.	Narrative literature review	The proposed mechanisms that mediate the connection between oral and systemic health include predisposing and precipitating factors (genetic, environmental, medications, microbial dysbiosis and bacteremias / viremias / microbemias and an altered host immune response).
[69]	Li et al. (2021)	To review recent advances in the infection hypothesis, in particular those pathogenic microbes that act systemically, through the periodontal and gastrointestinal infection pathways.	Narrative literature review	Convincing evidence that pathogenic microbial infection is associated with and is probably a causative trigger of AD pathology. Microbes can lead to AD pathology by two main routes: either by directly infecting the brain and stimulating amyloid-mediated defense (causative trigger) or indirectly by stimulating the pro-inflammatory effects of infection.
[70]	Olsen (2021)	To analyze whether *P. gingivalis* can contribute to Alzheimer's disease in the gingivitis stage.	Narrative literature review	Data have shown that it can take between 10 and 20 years for periodontitis to promote AD. It seems plausible that AD brain inflammation may begin early in the development of gingivitis, at least in severe generalized gingivitis, although PG abundance in gingivitis may be low. This may lead microglia to a pre-inflammatory phase,

				potentially promoting AD.
[71]	Romero et al. (2021)	To investigate the link between periodontitis and Alzheimer's.	Narrative literature review	Periodontopathogens produce an inflammatory response that, systemically, can trigger an inflammatory mechanism in the CNS. On the other hand, periodontitis may favor the formation of atheroma plaques that affect vascular integrity, suggesting a factor to be considered in the development of cerebrovascular disease.
[72]	Ryder e Xenoudi (2021)	To present biologically based evidence of the role of PD microflora in the initiation and progression of Alzheimer's disease.	Narrative literature review	More recent evidence indicates a possible role of the dental plaque microbiota associated with PD in the development and progression of AD, thus supporting a bidirectional interaction of these two diseases.
[73]	Sansores-Espanha et al. (2021)	To determine whether the pathology of AD and periodontitis may be associated, in order to allow greater knowledge of these diseases, which are so prevalent in the elderly.	Narrative literature review	There is not enough evidence to determine whether there is an association between these two pathologies, therefore it is considered necessary to carry out further studies to determine whether periodontitis is capable of inducing or exacerbating the neuroinflammation that will trigger AD.
[74]	Vigasova et al. (2021)	To highlight the potential role of multipathogen infections in AD.	Narrative literature review	A growing body of evidence suggests that the etiology of AD is driven, at least in part, by the coexistence of multiple pathogens (multimicrobial or polymicrobial hypothesis). However, more research is needed into AD from the point of view of the inflammatory polymicrobial microbiome.
[75]	Pisani et al. (2022)	To assess the progress scientists have made in clarifying the pathways by which bacteria enter the brain, as well as clarifying the mechanisms that support their travel from the oral cavity to the brain.	Narrative literature review	The eventual spread of bacteria to other areas of the brain affected by AD will cause neuroinflammation, stimulate lesion formation, and affect the permeability of the BBB to allow more oral bacteria, including PG, to enter the CNS via the

				bloodstream.
[3]	Lamphere et al (2023)	To explore potential mediators between periodontitis and Alzheimer's disease.	Scope review	Inflammation is an important mechanism in the onset and progression of periodontitis and Alzheimer's disease. However, more studies are needed to better understand the multifactorial pathogenesis of Alzheimer's disease

AD = Alzheimer's disease; PD = Periodontal disease; PG = *Porphyromonas gingivalis*; Mild Cognitive Impairment = MCI; BBB = Blood Brain Barrier; CNS = Central Nervous System.

Source: Prepared by the authors (2024).

Thus, based on a qualified and in-depth evaluation of the results of all 63 selected articles, it was possible to reach the following results. Some articles are repeated more frequently among systematic review studies and suggest the influence of Phorphyromonas gingivalis (PG) on Alzheimer's disease (AD) [20,31,70]. We also observed some common citations between the articles, as observed in article [20] which contains articles [42, 48 and 54], which were also cited in article [31]. These common articles describe the influence of PG on AD and, although they were published in different years, they converge on some points. Furthermore, several studies agree with each other and jointly conclude that periodontal infection plays a significant role in the innate immune regulation of AD, and further studies are needed to identify effective treatments for the early treatment of AD [9,13,14,19, 20,22,23,24,42,44,47,48,49,52,58,61,62].

On the other hand, narrative review articles [20,23,24] are the most prevalent of all the chosen studies and reiterate, in line with these other articles [63,64,65,66,67,70,73,74], the importance of evaluating neurodegeneration caused by Alzheimer's disease and its potential progression mediated by multimicrobial infections. At the same time, more recent evidence confirms the role of periodontal disease in the progression of Alzheimer's disease, although more specific studies are needed [72]. Thus, following this analysis, it is possible to perceive the multifactorial potential of these pathologies and thus understand a little about the different forms of correlation between them, also denoting the need for more in-depth and targeted studies.

4. DISCUSSION

This section followed the fifth stage called “analysis and interpretation of results” proposed in the study [17], which aims to analyze the association between periodontal disease and Alzheimer's disease.

Of the 63 studies included in this review, most were written in English [2,3,9,13,15,18-28, 30-72,74,75] followed by Spanish [29,73,76]. Of the studies analyzed, only seven involved animals (mice and dogs) [19,27,30,31,35,38,43] and were used to induce periodontitis. Forty studies were review studies: narrative literature reviews [48,54,61,66,67,68,69,70,71,74,75] systematic reviews [2,9,14,32,42,43,44,45,47,48,49,50,51,54,56,57,58,60]and scoping reviews [3].Followed by experimental studies with humans [13,25,26,27,28,30,32,33,35,36,37] and cross-sectional [23,34], descriptive and observational [18,24], as well as population-based cohort [39,40,41] or prospective [38,40,41] studies.

Unanimously, the results of the studies analyzed in this research point to evidence of an association between periodontal disease and Alzheimer's disease, with *P. gingivalis* being the pathogen most commonly involved in both. Also based on the studies analyzed, there are four strands to the results, as described below:

A) *P. gingivalis* and other periodontal bacteria play a role in the process of systemic inflammation that leads to inflammation of the cerebrospinal fluid and indirectly cause acceleration (trigger) for the onset and progression of Alzheimer's disease [19,20,26,27,28,30,42,43,44,45,47,50,53,56,58,61,64,69,70,71].

B) Although the inflammatory state in the oral cavity may be related to a brain degeneration syndrome such as dementia and AD, more studies are still needed to investigate the role of periodontal bacteria and PG (multimicrobial hypothesis) in the pathogenesis and worsening of AD. Thus, it is suggested that greater care be taken with oral hygiene in individuals suffering from AD and dementia [9,13,14,23,24,33,34,36,40,50,54,55,59,62,64,67,74].

C) Periodontal disease represents a factor in the progression (exacerbation) of Alzheimer's disease via induced pathogenic bacteria, since these individuals may have poor oral hygiene care, either due to forgetfulness or poor manual dexterity. Thus, strategies for the prevention and treatment of PD are indicated [18,28,29,34,35,37,41,42,49,52,63].

D) "Age and gender are important variables to consider when evaluating periodontal bone tissue, they also have significant effects on bone homeostasis and the immune system, gender-related oral health and differences in immune status, which goes directly against the association of periodontal disease and the cognitive decline of Alzheimer's disease"[31,39,51,57].

However, although current literature indicates that periodontal disease and chronic non-communicable diseases (systemic diseases) such as AD have a biunivocal relationship, the causal relationship still needs to be proven [76].

One of the articles points out the existence of biases in the results of some studies on the subject, since most do not follow the same methodology and parameters, which prevents the results from being compared. In addition, they report the absence of meta-analysis studies on the subject [2].

The mechanisms that mediate this relationship between oral health and systemic health include predisposing factors inherent to the host, such as genetic factors, environmental factors, medications, microbial dysbiosis, bacteremia/viremia/microbemias and an altered host immune response [68].

"Periodontitis is associated with generalized alterations in brain structure and function among middle-aged and elderly adults, with no signs of cognitive decline. These alterations have been found not only in brain regions involved in primary sensory-motor processing, but also in brain regions associated with higher-order cognition. Thus, periodontitis may be an important risk factor for age-related neurodegeneration and dementia. More longitudinal studies are needed to verify the potential contributions of periodontitis to age-related cognitive disorders such as AD" [77].

Previously published studies [1,10,12,72,78,79,80,81] have also shown an association between periodontal diseases and the pathogenesis and/or progression of Alzheimer's disease.

5. CONCLUSION

Analysis of the results of this integrative review leads us to consider that *P. gingivalis* and other periodontopathogens play a role in the process of systemic inflammation and may indirectly accelerate the onset and progression of Alzheimer's disease. Furthermore, given that periodontal disease may be a factor in the exacerbation of this disease via induced pathogenic bacteria, and that individuals with Alzheimer's may have poor oral hygiene care, either due to forgetfulness or poor manual dexterity, the need for prevention and treatment strategies for periodontal diseases is emphasized.

Current literature shows the association of periodontal diseases with different systemic conditions, such as cardiovascular disease, liver disease, diabetes, metabolic syndrome, obesity, eating disorders, rheumatoid arthritis, cancer and adverse pregnancy outcomes. However, there are still no conclusive studies with a high level of scientific evidence on the relationship between periodontal diseases and Alzheimer's, and new research is needed with more methodological rigor in terms of the methods applied and the criteria for diagnosing the pathologies, as a primary way of obtaining a better understanding of the association between these diseases.

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1.

2.

3.

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