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Review Article

Porphyromonas gingivalis, Neuroinflammation and Alzheimer's Disease

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Summary: The oral microbiota dysbiosis, as well as lifestyle, geographical location, drug consumption, and dietary habits, are involved in the incidence and progression of dementia, Mild Cognitive Impairment (MCI), and some diseases such as obesity, diabetes, cardiovascular disease, preterm birth, rheumatoid arthritis, cancer, inflammatory bowel disease, and neurodegenerative disease e.g., Parkinson's Disease (PD) and Alzheimer's Disease (AD). AD is the most common cause of neurodegenerative disorder in the elderly. Also, neuroinflammation is the most common cause of AD pathogenesis. This study investigated the possible relationship between *Porphyromonas gingivalis* (P. gingivalis) and Alzheimer's Disease. This review is based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. The oral microbiota comprised various microorganisms, such as fungi, archaea, and bacteria. *Porphyromonas gingivalis* (*P. gingivalis*) is one of the microorganisms, it stimulates host immune cells and releases cytokines, lysosomal enzymes, nitric oxide, and reactive oxygen species that lead to cell damage, apoptosis, and inflammation. Therefore, periodontal disease (PerioD) through systemic inflammation leads to some problems like the progression of MCI, production and aggregation of beta-amyloid (Aβ) and tau protein in the brain of the elderly population. In addition, some treatment methods could modulate the adverse effects of *P. gingivalis* like probiotic dietary supplements, maintaining personal hygiene, as well as gingipain inhibitors which modulate cytokines through blocked Aβ production, ApoE proteolysis, and reduced neuroinflammation. In addition, therapeutic compounds like COR388 and COR286, as gingipain inhibitors, prevent *P. gingivalis* colonization in the brain and have a beneficial action in some conditions like aspiration pneumonia, low birth rate, rheumatoid arthritis, PerioD and AD.

Keywords*: Porphyromonas gingivalis, Lipopolysaccharide, Inflammation, Alzheimer's Disease*

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INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of dementia, cognitive impairment, and memory loss in the over 65 aged population (uddin *et al*., 2019). Also, some features such as language and visuospatial dysfunction appeared in later stages that lead to difficulties in daily activities and quality of life (Lane *et al*., 2018). Other complications following AD include blood clots, skin infections, and organ failure that can be destructive and fatal (Jia *et al*., 2020).

AD pathology is characterized by senile plaque formation with, abnormally folded beta-amyloid (Ab) protein on the outside of neurons and hyperphosphorylated Tau proteins on the inside of neurons (Ando *et al*., 2020; Coomans *et al*., 2021) which caused brain neurodegeneration (Yu *et al*., 2020). Recently, studies investigated the possible relationship between periodontitis and the initiation or/and progression of AD (Liccardo *et al*., 2020). Also, in recent years, researchers have been investigating the way to modify the moiety of chemical drugs with compatible substances like herbal drugs, nano-medicine and stem cells for AD therapy (Malekzadeh *et al*., 2017,2019, 2021).

Periodontal disease (PerioD) is a chronic infection, oral inflammatory, and bacterial condition that causes cancer or systemic disease and affects other organs like joints, heart, liver, and brain in 50% of the elderly population. Recently, researchers found a relationship between PerioD and dementia/cognitive impairment (Nazir, 2017). Also, to date, no evidence has validated periodontal bacteria as an AD biomarker. There are about 700 species of bacteria that colonize the subgingival biofilm and among them are periodontal bacterial species. These species comprise

Treponema denticola, Fretibacterium fastidiosum, Tannerella forsythensis, Campylobacter rectus, Fusobacterium nucleatum, Prevotella spp, *Porphyromonas endodontalis*, and *Porphyromonas gingivalis*. Other bacteria species involved in periodontal health are Veillonella, Rothia, Actinomyces, Corynebacterium, Capnocytophaga, and Streptococcus (Hajishengallis, 2014; Griffen *et al*., 2012). A study showed the association between PerioD and brain Aβ load through (11C)-PiB-PET (Pittsburgh compound-B positron emission tomography) in normal elderly (Kamer *et al*., 2015).

Furthermore, studies have shown that saliva is a promising source for early AD detection; so far, salivary proteomics tests have been performed for the detection of periodontal disease as well as oral cancer (Wu *et al*., 2015). Also, a study showed that salivary proteome changed with ageing diseases such as AD and detectable Ab and tau markers in salivary glands. Interestingly, saliva and CSF participate in the same 288 target proteins with 27 of those directly associated with AD (Manconi *et al*., 2017). A study showed that CSF and blood Transthyretin (TTR) gene levels are inversely related to the severity of AD. Also, mutations in the TTR gene have been shown to cause liver amyloidosis (Adams *et al*., 2019) and MCI (Bermejo-Pareja *et al*., 2010).

It has been shown that the level of neopterin and tryptophan (immune activation and modulation biomarkers) are important in cancer and AD. Increased neurotoxic levels of tryptophan cause an increase in the catabolism of quinolinic acid and cognitive impairment in AD conditions (Leblhuber *et al*., 2017; Giil *et al*., 2017).
It has also been shown that patients with a positive sign of a periodontal, low number of teeth, and APOE4 (apolipoprotein E4) allele carriers displayed more rapid cognitive dysfunction with time-dependent compared with normal subjects (Sparks *et al*., 2012).

MATERIALS AND METHODS

This study was based on research studies indexed in Scopus, Science Direct, PubMed, and Google Scholar databases. Also, keywords used during the search include: "*Porphyromonas gingivalis*", "Lipopolysaccharide", "*P. gingivalis* and Alzheimer's Disease", "*P. gingivalis* and neurodegenerative disease", "gingipain inhibitors and Alzheimer Disease".

RESULTS

1-Alzheimer's disease and inflammation: A study suggested that brain inflammation is related to AD pathogenesis (Rogers *et al*., 1996). The evidence showed that the risk of AD among rheumatoid patients (due to long-term use of non-steroidal anti-inflammatory drugs (NSAIDs)) is reduced (McGeer *et al*., 1996). In AD patients, Aβ accumulation causes an inflammatory response, neuronal damage, and synaptic damage. Also, one factor which regulates the inflammatory response is TREM2 gene which is increased in AD patients (Cao *et al*., 2018). On the other hand, neuroinflammation and CNS infection are related to altered microglia levels. Aβ and Bacterial lipopolysaccharide (LPS) cause microglia activation with phagocytosis ability, thereby eliminating injured nerve cells, and releasing some factors including chemokines, cytokines, and BDNF. In addition, the excessive release of cytokines causes neuropathy. Accumulated active microglia cells are present in the injured site in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease (Rojanathammanee *et al*., 2015). In AD patients, Tumor necrosis factor (TNF)-α level is increased and related to cognitive dysfunction (Alvarez *et al*., 2007).

Studies have shown that Glycogen synthase kinase-3 (GSK3β) is an important key factor in neurogenesis, memory formation/consolidation, long-term depression (LTD), and long-term potentiation (LTP). Activation GSK3β inhibited LTP dysfunction and modulated LTD in AD subjects. Also, GSK3β, pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF-α), and other cytokines (such as IL-1α/β and IL-6) are involved in neuroinflammation. Furthermore, microglia (the brain immune cells) are responsible for much pro-inflammatory cytokines production and neuroinflammation (Lauretti *et al*., 2020).

The mechanism of *P. gingivalis* and AD: P. gingivalis-LPS and lipopolysaccharide (E. coli -LPS), as Gram-negative bacteria, have some structural and functional differences. E. coli –LPS cause cognitive dysfunction in mice through TLR4/NF-κB signalling pathway (Zhang *et al*., 2018). There is an existence of P. gingivalis–LPS in Alzheimer's disease brain autopsy, suggesting a possible link between P. gingivalis–LPS and cognitive dysfunction (Olsen and Singhrao, 2020).

A study investigated P. gingivalis–LPS infection in mice (C57BL/6) and cognitive function through Morris water maze (MWM), open field test (OFT), and passive avoidance test (PAT) (Zhang *et al*., 2018). Immunohistochemistry analysis showed the activation of microglia and astrocytes in the hippocampus and cerebral cortex. The findings of the study also showed that P. gingivalis–LPS caused memory loss, learning impairment, and cognitive dysfunction in C57BL/6 mice; suggested by activation of the TLR4 signalling pathway. Studies showed dementia/cognitive impairment is related to inflammation including, C-reactive protein, IL-1, TNF-α, IL-1, and IL-6 (Zhang *et al*., 2018; Hoozemans *et al*., 2003). Also, non-steroidal anti-inflammatory drugs (NSAIDs) decreased the incidence of AD (Lim *et al*., 2013).

In addition, microbes (e.g., Borrelia burgdorferi and Chlamydia pneumoniae) are associated with dementia/cognitive impairment that is displayed in blood and cerebrospinal fluid samples of AD subjects (McGeer *et al*., 2018). One case report suggested infected subjects were approximately 2 times more than normal subjects suffer from dementia (Dunn *et al*., 2005).

Though, one study showed periodontitis and dementia are not related. Also, one study revealed periodontal pockets with more than 4 mm in more than one tooth of subjects cause a higher risk of dementia (approximately 1.5 times of the normal group) (Maldonado *et al*., 2018; Tiisanoja *et al*., 2019). In addition, oral bacterial species studies have shown that the levels of IgG antibodies are related to periodontitis and AD onset/progression (Stein *et al*., 2012).

A study involving 947 elderly subjects with gingival inflammation revealed cognitive decline through Mini-Mental State Examination within 2 years (Stewart *et al*., 2013). One study showed that severe periodontal disease

mostly causes cognitive decline within 5 years (Iwasaki *et al*., 2019). Another follow-up study showed 558 adults aged 52-75 years (within 8 years) have no significant differences in periodontal disease compared to healthy subjects (without periodontal disease) in terms of cognitive impairment (Naorungroj *et al*., 2015). Another study showed gingival bleeding (as an active inflammation index) was associated with cognitive impairment (Stewart *et al*., 2008). The high-quality nested case-control study showed the subjects with dementia and mild cognitive impairment and dementia had more periodontal antibodies (Stein *et al*., 2012).

Studies demonstrated that α-1 antichymotrypsin, C-reactive protein, and interleukin 1b, 2, 6, and 18 increased in Alzheimer's disease (Lai *et al*., 2017). The high level of C-reactive protein and interleukin-6 are related to an increase in the risk of AD (45% and 32%, respectively) (Koyama *et al*., 2013). Also, these proinflammatory molecules are used as a delirium index in AD (Plas *et al*., 2018).

It has been shown that the dysregulation of IGF-I/PI3K/AKT/mTOR signalling caused impairment of immune functions, synaptic plasticity, social interactions, myelinization, and learning (Chen *et al*., 2014). On the other hand, NOTCH, FoxO, and NGF pathways play an important role in CNS neurodevelopment, synaptic plasticity, neurogenesis, behaviour, learning and memory (Hwang *et al*., 2018). The CD14 cells could be activated by LPS of bacteria and released to the circulation system and choroid plexus, therefore, causing leptomeninges and brain inflammation in AD areas (Abbayya *et al*., 2015).

The importance of investigating the role of *P. gingivalis* in AD: The incidence rate of gingival and periodontal infections through *P. gingivalis* in healthy subjects is 25%; infections could occur during daily life and activities such as; dental procedures, flossing, brushing, and chewing (Griffen *et al*., 1998). Also, infections could transit into the liver, coronary arteries, and placenta. The high rate of gingival and periodontal infections among cardiovascular patients has been proven.

P. gingivalis is an asaccharolytic Gram-negative anaerobic bacterium which releases cysteine proteases named gingipains (Grenier *et al*., 2001; Li *et al*., 2011). Some of the commonly released gingipains are; arginine-gingipain A (RgpA), arginine-gingipain B (RgpB), and lysine-gingipain (Kgp). These factors (Kgp and RgpA/B) are important for *P. gingivalis* pathogen survival, colonization, and demolition of host defences and consumption of iron and nutrient (Dominy *et al*., 2019; Arastu-Kapur *et al*., 2020). Then, Gingipains spread through the extracellular milieu and outer membrane vesicle (OMV) into fibroblasts, epithelial cells, and endothelial cells. Administration of short peptide analogues have been reduce *P. gingivalis* virulence and blocked gingipain proteolytic activity. Also, *P. gingivalis* DNA in CSF and the brain of AD patients suggests it could use as a diagnostic marker (Guo *et al*., 2000; Gui *et al*., 2016; Grenier *et al*., 2003).

Brain gingipain load in middle temporal gyrus (MTG) as AD diagnostic marker: Immunohistochemical (IHC) studies correlated with tissue microarrays (TMAs) techniques which can measure and compare studies of the middle temporal gyrus (MTG) brain tissue cores in AD and normal individuals showed Gingipain antibodies, CAB101 and CAB102 (Haditsch *et al*., 2020). These antibodies specifically target RgpB (as non-phosphorylated tau) and Kgp (as phosphorylated tau), respectively, and it is used for determining brain tissue cores of gingipain load. The assessments of AD samples showed 96% RgpB positive and 91% Kgp positive staining that suggested AD brains have a significantly higher load of RgpB and Kgp compared to healthy samples. Also, they showed a relation between RgpB load and tau load or Kgp load and tau load that suggested the association between those and cognitive impairment (Dominy *et al*., 2019; Jungbauer *et al*., 2022).

On the other hand, the assessments of ubiquitin (small regulatory protein (8.6 kDa) in eukaryotic organisms tissue which is vulnerable to proteasomes and used as a marker of proteasomes attack and infection) showed the high-level accumulation of ubiquitin around tau tangles and Ab plaques through TMAs. It's notable that, 39% RgpB positive and 52% Kgp positive staining were detected in non-demented control samples (Rajmohan *et al*., 2017; Dominy *et al*., 2019).

Also, studies have revealed the correlation between gingipain load and tau load / and gingipain and ubiquitin load in non-demented control samples which suggested a continuum of gingipain and AD pathology in non-demented control samples at the primary stage of preclinical AD without clinical symptoms. Therefore, brain RgpB and Kgp antigens have a positive correlation with tau load, ubiquitin load, and AD diagnosis (Mao *et al*., 2022). In addition, RgpB immunostaining of MTG showed no significant differences in amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease samples compared with the control group (Spudich *et al*., 2005).

***P. gingivalis* 16S rRNA and hmuY genes in AD cerebral cortex as AD diagnostic marker:** Brain lysates and Kgp were detected in the grey matter of the cerebral cortex of AD patients. The quantitative polymerase chain reaction (qPCR) analysis confirmed the expression of *P. gingivalis* 16S rRNA gene in AD brains through hmuY gene primer which suggests that the genes are highly specific for P. gingivalis. To prevent the effects of low copy numbers of *P. gingivalis* DNA and maybe cause a false-positive signal of nested amplification, the researchers used another ubiquitous Gram-negative bacterium, Helicobacter pylori. Then in the same numbered samples of *P. gingivalis* and H. pylori that revealed negative for H. pylori through qPCR primers and probes in AD samples; that means *P. gingivalis* specifically related to AD. Therefore, *P. gingivalis* DNA was detected in AD sample brains (Spudich *et al*., 2005).

Periodontitis is described as the deep periodontal pockets which caused loss of the connective tissue attachment and alveolar bone. Adult oral cavities have the most microbiota after the gut (Könönen *et al*., 2019). The cavity has over 700 species of microbiota and the subgingival plaque has up to 400 species which are divided into nine bacterial phyla (Aas *et al*., 2005).

The most common periodontal pathogens include Treponema denticola, Tannerella forsythia, and *Porphyromonas gingivalis* (the so-called ''red complex'' bacteria) which is related to clinical features of chronic periodontitis. Mostly, *P. gingivalis* is a heme auxotroph. For survival, *P. gingivalis* need heme uptake from the host

environment through hmu system which is comprised of five additional proteins and the HmuY hemophore (Sheldon *et al*., 2016; Gmiterek *et al*., 2013). Usually, the 16S ribosomal RNA gene (16S rRNA)is used in bacteria detection studies because the nucleotide sequences are preserved among many bacterial species.

Presence of *P. gingivalis* DNA in the cerebrospinal fluid (CSF) as AD diagnostic marker: CSF, as a window of brain infection (Spudich *et al*., 2005), has a crucial role in the functioning of the brain including brain cushioning, intracranial pressure maintenance, nourishment, and detoxification. Therefore, CSF microbes reveal important information about CNS and brain functioning; although detection of CSF microbes may not always indicate CNS infection. In addition, the existence of microorganisms may be related to CNS diseases such as MS and AD. Approximately 500 ml of CSF are produced per day (150 ml of CSF in CNS). Then CNS infection appeared in CSF and PCR of CSF is the first detection manner in CNS infection analysis (Yamamoto *et al*., 2002). The analysis of hmuY gene in CSF and saliva by qPCR positive *P. gingivalis* DNA and negative H. pylori. Therefore, CSF analysis can be used to confirm the existence of *P. gingivalis* infection in the brain of AD patients (Gmiterek *et al*., 2013).

The neuroprotective compounds against P. gingivalis

1-4- Oral Microbiota Modulation and Alzheimer's Disease Therapy: Probably, the mechanisms of *P. gingivalis* and its related toxin are transferred from blood–brain barrier (BBB) into the brain and the hematogenous route (Nonaka *et al*., 2022). *P. gingivalis* infection reduces cognitive function. Periodontitis is the most cause of teeth loss and a risk factor for AD. As a result of teeth loss, there is a reduction in chewing function and the cerebral blood flow which leads to cognitive function impairment (Oue *et al*., 2016; Okamoto *et al*., 2015).

Also, a study showed that APP-transgenic mice have a reduction in cognitive function as well as deposition of Aβ, however, brain inflammation was not found (Oue *et al*., 2013). Although other studies showed a relationship between APP transgenic mice model, *P. gingivalis* inflammation (periodontal disease), increased cerebral Aβ deposition, and decrease cognitive function (Matsushita *et al*., 2020). The studies suggested that cognitive decline causes loss of teeth and periodontal disease, and decreased number of hippocampal neural cells through reduction of BDNF signalling (Oue *et al*., 2016). Also, chewing dysfunction and liquid diets were shown to induce memory and cognitive impairment (Okihara *et al*., 2014).

A study investigated the effects of phototherapy on the modulation of the oral microbiome and its possible application to the treatment of AD (Soukos *et al*., 2015) The study showed that blue light is fast, painless, and did not exhibit toxicity while it reduced oral dysbiosis in PD and AD patients (Jo *et al*., 2022). Probiotic strains (such as yoghurt, milk, and mouthwash) affected periodontogenic and lead to increase AD oral hygiene levels (Allaker and Stephen, 2017).

Pathological modulation of AD including, mitochondrial dynamics regulation, reduction of amyloid-β aggregation, and increased neuronal energy is associated with metabolic pathways (e.g., Wnt signalling, 5'-adenosine monophosphate-activated protein kinase) (Maitre *et al*., 2021).

Small-molecule gingipain inhibitors as neuroprotective agents: The levels of *Porphyromonas gingivalis* (Pg), as a bacterial pathogen, and its protease (gingipains) increased in AD brain suggesting a correlation between Pg and neurodegeneration pathology (Kim *et al*., 2021). Interestingly, the oral administration of gingipain inhibitor (COR388) possesses a neuroprotective effect against AD through blocked lysine-gingipain and regulation of immune response; which proved the effects of gingipain in AD pathology. Mass Spectrometry (MS) analysis near the gingipain cleavage sites and the protein carboxy-terminal in ApoE4 carrier confirmed that gingipain inhibitors have an important role in the blocking and cleavage of ApoE proteolysis. COR388 administration increased the low-molecular-weight (LMW) fragments of proteolytic ApoE4 cleavage in CSF of AD patients compared with those of non-AD subjects within 28 days (Raha *et al*., 2020). For a better understanding of gingipain cleavage sites within tau, which colocalizes together, SH-SY5Y cells were used as tau forms with high–molecular weight expression and Tau-5 antibody as a probe (Aquilano *et al*., 2010).

The results showed the association of SH-SY5Y cells (in *P. gingivalis* infected model) and produced tau protein. Also, treatment with gingipain inhibitors showed approximately 50% of *P. gingivalis* cells death. The oral administration of COR286 (the RgpB inhibitor), as gingipain inhibitor, was effective in blocking *P. gingivalis* through the hippocampus within 10 weeks; but COR271 (the Kgp inhibitor) did not reduce the bacterial within 5 weeks (Dominy *et al*., 2019; Portelius *et al*., 2012).

DISCUSSION

Studies demonstrated the relation between periodontitis and systemic diseases including, respiratory disease, cardiovascular disease (Dietrich *et al*., 2013; Tonetti *et al*., 2013), adverse pregnancy outcomes (He *et al*., 2015), diabetes (Chapple *et al*., 2013), cancer and nervous system diseases (Noble *et al*., 2009; Perera *et al*., 2016). In addition, 10 year follow-up study showed periodontitis led to an increased risk of AD (Chen *et al*., 2017). Also, the host microbiota may cause the accumulation of beta-amyloid. In addition, intestinal microbiota and "Microbiota-gut-brain axis" are associated with Ab aggregation, brain dysfunction, and AD progression (Doifode *et al*., 2021).

Inflammation is the most common cause of AD pathogenesis as activated microglia produces pro-inflammatory cytokines which lead to increases in the levels of b-amyloid, p -Tau production and neurodegeneration through paracrine and/or autocrine pathways (Cai *et al*., 2014). Other studies also showed that chronic bacterial infections, such as tuberculosis, syphilis, leprosy, osteomyelitis, and rheumatoid arthritis cause amyloid accumulation and impairment of cognitive functions (Ishida *et al*., 2017).

Studies showed the track of *Porphyromonas gingivalis* infection and lipopolysaccharide in AD subject brains (microglial cells and hippocampus) of mice. In this regard, the existence of *P. gingivalis* lipopolysaccharide (LPS) in autopsied AD brain tissues is proof because it is not seen in

normal human brain tissues (Lee *et al*., 2008). On the other hand, in ApoE knockout mice, *P. gingivalis* could enter the brain which means the possible mechanism of *P. gingivalis* may be independent of ApoE and may be related to beta-amyloid (Xuan *et al*., 2017). Another possible mechanism of *P. gingivalis* is related to its ability to bind to E-selectin through its OmpA-like protein and to activate the small G-protein Rab5 and the intercellular adhesion molecule (ICAM)-1 in host cells (Kato *et al*., 2014).

The studies have shown that small molecule gingipain inhibitors have neuroprotective effects against brain neurotoxicity and neuroblastoma cell line in vitro and also in wild-type mice (Dominy *et al*., 2019). In comparison to antibiotics, gingipain inhibitors prevented and mitigated the toxic effect of *P. gingivalis* in cell culture, whereas some antibiotics (moxifloxacin, doxycycline, and semagacestat) that inhibit beta-amyloid production could not. Furthermore, mice infected with *P. gingivalis* had reduced DNA. (Xuan *et al*., 2017) as well as an increased inflammatory mediator -tumor necrosis factor-α and beta-amyloid in the brain.

The studies suggest that gingipain inhibitors could be a promising therapy for the treatment of both periodontitis and AD; because periodontitis and AD may originate from the same usual factors like genetic susceptibility, infectious agents, lifestyle and so on. Also, *P. gingivalis* proteases (gingipain) are associated with beta-amyloid, tau tangles, and neurons and administration of gingipain mediated beta-amyloid and cognitive function. The underlying factors mediating the effects of periodontitis on AD is not yet clear but *P. gingivalis* could induce AD. Some AD patients have *P. gingivalis* infection. Also, it is good to know which factors play a key role in the pathophysiology of AD, is it age, tobacco use or genetics? The studies also sought to uncover the mechanisms of how pathogens cause the development of periodontitis or treatments that could be useful for ameliorating AD and the progression of MCI (Ryder, 2020).

Indeed, neuroinflammation is a common pathogenic factor in neuropsychiatric disorders and periodontitis (Hashioka *et al*., 2019). Periodontitis increases peripheral pro-inflammatory cytokines and initiates systemic inflammation and neuroinflammation through neural, humoral and cellular pathways. In neural pathways, cytokines activate afferent nerves, such as the vagus nerve as well as hypothalamic brain nuclei. Periodontitis could be transferred through the humoral pathway which involves the circumventricular organs, and choroid plexus where the lack of a contiguous blood-brain barrier (BBB). Then pro-inflammatory cytokines may enter the cerebral parenchymal through volume diffusion and alter brain functions (D'Mello *et al*., 2016). The cellular pathway starts from systemic inflammation and it may involve endothelial cell (CECs) activation and a high level of circulating monocytes. Therefore, expression of TNF-α and IL-1β cause perivascular macrophages to increase in CECs area and activated microglia. Activated microglia secrete not only pro-inflammatory cytokines but also chemokines and proteases, including monocyte chemoattractant protein (MCP)-1. MCP-1 recruits the monocytes into the motor cortex, hippocampus, and basal ganglia region. These regions are involved in the regulation of behaviour (D'Mello *et al*., 2009).

Periodontal bacterial enter the brain through the bloodstream and cranial nerves. In periodontitis, as bacterial molecules increased in a periodontal pocket, periodontal bacteria invade the pocket epithelium and enter the circulation (Kamer *et al*., 2008; Olsen *et al*., 2015; Riviere *et al*., 2002).

The leptomeninges can host periodontal bacteria; the leptomeninges covers the brain parenchymal and forms a physical boundary with the cerebrospinal fluid (CSF)-blood barrier; the leptomeningeal cells express Toll-like (TLRs) 2 and 4 receptors for P. gingivalis. LPS. Leptomeningeal cells can be activated by circulating *P. gingivalis* LPS to produce brain pro-inflammatory cytokines (Liu *et al*., 2013; Wu *et al*., 2005). Therefore, microglia are activated and neuroinflammation occurs. Furthermore, a study showed that a high level of *P. gingivalis* IgG leads to delayed verbal memory and subtraction impairment in AD patients (Noble *et al*., 2009). Also, the cognitive ability of AD patients could be modified in response to the presence of confounding factors (such as age and smoking) which may be out rightly not related to P. gingivalis. (Sparks *et al*., 2012).

Chronic *P. gingivalis* infection within 5 consecutive weeks leads to Aβ accumulation in neurons, microglia-mediated neuroinflammation, and learning and memory deficits in mice models through cathepsin B (CatB) signalling. CatB plays an important role in peripheral Aβ generation. *P. gingivalis* infection increased the CatB/NF-κB-dependent receptor for advanced glycation end (RAGE) expression in cerebral endothelial cells, which crosses peripheral Aβ into the brain (Nie *et al*., 2019).

CONCLUSION

Periodontal disease is the inflammation of periodontal tissue (gum, bone and periodontal ligament) and the earlier stage - gingivitis (inflammation of the gum at the neck of teeth) are inflammatory conditions which may lead to diseases such as osteoporosis, diabetes, cardiovascular disease, and mental disorders. Achieving good oral hygiene, dieting with minimum sucrose, quitting smoking and/or alcoholism, and boosting the immune system lead to a healthy oral microbiome. Also, gingipain inhibitor is effective in blocking *P. gingivalis* and reduces the adverse effect in AD patients or those with MCI conditions.

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