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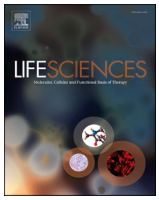

Implications of gut and oral microbiota in neuroinflammatory responses in Alzheimer's disease

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ABSTRACT

A diverse and stable microbiota promotes a healthy state, nevertheless, an imbalance in gut or oral bacterial composition, called dysbiosis, can cause gastrointestinal disorders, systemic inflammatory states and oxidative stress, among others. Recently, gut and oral dysbiosis has been linked to Alzheimer's disease (AD), which is considered the most common form of dementia and a public health priority due to its high prevalence and incidence. The aim of this review is to highlight the implications of gut and oral microbiota in the neuroinflammation characteristic of AD pathology and the subsequent cognitive impairment. It is a systematic review of the current literature obtained by searching the PubMed, Web of Science and Scopus databases. The characteristic intestinal dysbiosis in AD patients leads to increased permeability of the intestinal barrier and activates immune cells in the central nervous system due to translocation of microbiota-derived metabolites and/or bacteria into the circulation leading to increased neuroinflammation and neuronal loss, thus generating the cognitive impairment characteristic of AD. The presence in the central nervous system of *Porphyromonas gingivalis* can cause an increased neuroinflammation and beta-amyloid peptide accumulation.

1. Introduction

The human body is colonized by 10 to 100 trillion microorganisms, including bacteria, fungi, archaea and viruses [1,2]. This biological community is called the microbiota [1]. The intestinal tract is the most colonized organ, housing 95 % of the microorganisms [3], followed by the skin which is colonized by about 10^{12} microbes, and the rest cohabit in various areas of the human body such as the vagina, urinary tract, hair and nostrils [1]. Also, oral cavity has a complex ecosystem in which around 700 species of bacteria coexist [4].

The microbiota maintains a symbiotic relationship with the human host; it can interact in a beneficial, neutral or detrimental way to the host and consequently play regulatory roles in both health and disease [2]. The microbial population is in a continuous and delicate balance but can be affected by various factors such as lifestyle, hormones, diet, genetics, metabolism, infections and immune responses [5]. In general, a diverse and stable microbiota establishes a mutualistic relationship with the human host, promoting human health [6]; however, an imbalance in gut or oral microbial composition, termed dysbiosis, disrupts the host-microbe symbiosis which can cause gastrointestinal disorders, low-grade inflammatory states, increased oxidative stress and cellular deterioration [5,7]. In recent studies, gut and oral dysbiosis has also been associated with neurodegenerative diseases [4,8–10].

1.1. Gut- microbiota–brain axis

The gastrointestinal tract exerts an influence on the brain and vice versa. The central nervous system (CNS) is composed of afferent and efferent autonomic pathways to communicate with muscle and the intestinal mucosal layer to work on intestinal motility, secretion and intestinal mucosal immunity [5]. The enteric nervous system (ENS) is the nervous system that regulates the gastrointestinal tract. Its neurons are organized in microcircuits that modulate gastrointestinal function independent of the CNS, although both systems are linked and influence each other [11]. The pathway between the microbiota, the gut and the CNS arises through what is called the "gut–microbiota-brain axis" [12].

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This axis involves other systems such as the autonomic nervous system, the endocrine system, the hypothalamic–pituitary–adrenal axis, the immune system and the microbiota and its metabolites [13,14]. This connection is established by neurons, hormones and other neuroregulatory factors. The gut–brain axis facilitates a bidirectional communication between the two organs mainly by through neuronal messages carried by afferent pathways of vagus nerve [12,13]. The vagus nerve is the main channel of communication between the brain and the gut. It is composed of 20 % efferent fibers and 80 % afferent fibers [15]. Thus, the afferent branch of the vagus nerve is the main neural pathway of the CNS, linking the intestinal tract with the brain, exactly with the nucleus of the solitary tract located in the medulla oblongata. The vagus nerve does not appear to interact with the gut microbiota directly, but it can detect microbial signals in the form of bacterial metabolites [16].

Bacterial strains influence the CNS by producing neurotransmitters such as catecholamines, gamma-aminobutyric acid (GABA), glutamate, norepinephrine, dopamine, acetylcholine, histamine and other neuromodulator substances, including short-chain fatty acids (SCFAs) and long-chain fatty acids (LCFAs), propionate, linoleic acid linked with bacterial metabolites affecting the host physiology [5,17,18], which influence the behavior of glial cells in both the CNS and the ENS [19,20]. Thus, the gut microbiota has emerged as an environmental factor that can modulate the CNS and ENS [1]. In turn, the microbiota contributes significantly in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) [16], which is considered the most common cause of dementia and a public health priority [21].

1.2. Oral-microbiota-brain axis

Several species of microorganisms have been identified in the oral microbiota ecosystem, bacteria such as *Streptococcus*, *Neisseria*, *Veillonella* and *Actinomyces* predominate. The oral microbiota exists as biofilms throughout the oral cavity, forming an ecosystem homeostasis that maintains health [22]. Therefore, oral dysbiosis may alter the function of the bacterial community and have a significant impact on health [7].

Two of the major dental diseases caused by a dysbiosis of oral microbiota are dental caries and periodontal disease (PD) [23]. The latter is an inflammatory disease characterized by a progressive destruction of the tissues of the periodontal complex, mediated by a bacterial dysbiosis predominated by gram-negative anaerobic bacteria such as *Porphyromonas gingivalis*, *Actinobacillus actinmycetemcomitans* and *Tannerella forsythia* [4,24,25]. PD is a multifactorial disease, although oral hygiene or lack thereof, is a determining factor for the onset of the disease [26]. In general, PD is thought to induce a systemic inflammatory response, due to the propagation of bacteria and inflammatory mediators from periodontal tissues into the bloodstream. Once bacteria circulate at the blood level, they can cross the blood-brain barrier and damage central nervous tissues [22,27]. Even oral microorganisms can gain access to the CNS via the trigeminal nerve which connects to the brain [22]. In the trigeminal ganglion there are glial cells that produce significant levels of inflammatory cytokines and are capable of recognizing bacteria, engulfing, processing and presenting them to the T lymphocytes. Pathogenic bacteria have the ability to inhibit phagolysosome. They can remain alive within the phagosome and, through vesical trafficking, can move along the axon or dendrites of the neuron [10]. Therefore, the brain can undergo different inflammatory processes that contribute to development of AD. Indeed, inflammation is viewed as the link between PD and AD [24,27,28].

1.3. AD and its pathology: Neuroinflammation

AD, first described in 1906 by Alois Alzheimer, is a primary neurodegenerative disease [20,29,30], mainly characterized by abnormal processing and oligomerization of normally soluble proteins. These attain altered conformations due to genetic mutations, external factors or the ageing process and aggregate, leading to neuronal loss [30].

The etiology of AD is still unknown. There are autosomal dominant mutations in amyloid precursor protein (APP) gene and in presenilin 1 and 2 gene (PSEN1 and PSEN2) that cause what is termed familial AD, in which symptoms appear between the ages of 30 and 50 years [21] and account for the majority of cases of dominant inheritance in AD [29]. However, 99 % of all cases of AD occur in a late-onset sporadic form after the age of 65 in which genetic and environmental factors interact [21]. Within the sporadic form of AD, apolipoprotein E (APOE) is a susceptibility polymorphism and the most relevant genetic risk factor in AD. Having the ε4 allele of APOE increases the risk of developing AD compared to the APOE-2 and APOE-3 isoforms [31]. The genetic factor has been studied to account for 70 % of the risk of developing AD. However, multiple external risk factors have been investigated, including medical and psychiatric factors such as cardiovascular disease, obesity, dyslipidemia, depression and stress, as well as environmental factors including pollution, some metal and vitamin deficiencies, and lifestyle factors such as smoking, physical exercise and diet [32,33]. Microbial dysbiosis is linked to all these factors [1].

AD pathology is characterized by the presence of intracellular senile plaques (SPs) formed by beta-amyloid peptide with a chain length of 42 amino acids (Aβ42) [30] and extracellular neurofibrillary tangles formed by hyperphosphorylated Tau protein in AD patients [29,34]. Other associated changes in AD pathology include neuroinflammation and brain atrophy [35].

Neuroinflammation is the CNS's inflammatory response preceded by neuronal damage. This process is characterized by the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), as well as chemokines like C—C motif chemokine ligand 1 (CCL1), CCL5 and C-X-C motif chemokine ligand 1 (CXCL1). Additionally, small molecule messengers such as prostaglandins and nitric oxide (NO) are generated, along with reactive oxygen species, by innate immune cells within the CNS. The innate immune cells involved in this process are primarily microglia and astrocytes, but capillary endothelial cells and infiltrating blood cells also contribute to neuroinflammation, especially when the blood-brain barrier sustains biochemical or mechanical damage [36–38].

Microglial cells function like macrophages, that become activated during ageing [37]. However, in response to damage to the CNS, such as injury or infection, microglia are activated to produce pro-inflammatory or anti-inflammatory factors [39]. Macrophage activation encompasses a broad spectrum of functional states by the recognition molecular patterns from lipopolysaccharides (LPSs), which are components of the bacterial wall, and viral capsid proteins to debris released by dead cells and beta-amyloid peptide oligomers [40]. The best known activated pro-inflammatory substances in AD are IL-1β, IL-6 and TNF-α [8,37,39,40].

Astrocytes are specialized glial cells, originating from neuroepithelium, which form the framework of the entire CNS [14,38]. It is responsible for removing neurotoxic products, including beta-amyloid peptide and Tau protein [38] so their role has been significantly highlighted in AD, especially for the regulation of neuroinflammation [10].

However, CNS neuroinflammation may originate from inflammasomes, which are multi-protein complexes that mediate innate immunity. In the CNS, the inflammasome is predominantly found in the cytoplasm of immune cells, neuronal cells, astrocytes and microglia, where it recognizes pathogen-associated molecular patterns (PAMPs) or host-derived danger-associated molecular patterns (DAMPs). Based on the receptor structure, sensors can be classified into two types: nucleotide-binding oligomerization domain-like receptors (NLRs) and absent in melanoma 2 receptors (ALRs) [41,42].

The most extensively studied classes of inflammasomes are represented by the inflammasome-forming NLRs, including NLRP1, NLRP3, NLRC4, NLRC5, NLRC6, NLRP6, NLRP7 and NLRP12. Among these, the one most closely associated with AD is the nucleotide-binding domain, leucine-rich repeat protein-3 (NLRP3) [42,43]. NLRP3 belongs to the NLR family and includes the sensor protein NLRP3, the adaptor protein

apoptosis-associated speck-like protein containing caspase activation and recruitment domain (ASC), and the effector protein (pro-caspase-1, a cysteine protease) [44]. The activation of the NLRP3 inflammasome contributes to the conversion of procaspase-1 into active caspase-1, resulting in the production of proinflammatory cytokines IL-18 and IL-1β [43].

Nevertheless, oral microbiota dysbiosis is purported to contribute directly to peptide beta-amyloid production through the trigeminal nervous system and circulating blood. It can also occur through gut microbiota and their products, which can affect the brain directly through the ENS and CNS [45,46]. Metabolites generated by the gut microbiota can penetrate the gut wall and influence the behavior of glial cells in both the ENS and the CNS [16,22].

The aim of this systematic review is to examine by means of a systematic review the implication of gut and oral microbiota in the neuroinflammation characteristic of AD, with subsequent cognitive impairment.

2. Methods

2.1. Data sources and search strategy

A systematic literature search was conducted to explore the relationship between oral and gut microbiota dysbiosis and AD, particularly in the context of neuroinflammation and cognitive impairment.

The present systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 (PRISMA, 2020) as a reporting guideline [47]. It was carried out by means of a search strategy, represented in Fig. 1, using PubMed, Scopus and Web of Sciences databases with access date between August of 2022 and August of 2023.

The following search terms were used to identify eligible studies: (Alzheimer's disease) AND (gut microbiota OR oral microbiota OR dysbiosis OR neuroinflammation OR NLRP3 protein).

The search was limited to articles published in English within the date range January 2018 to August 2023 to ensure a focus on the most recent and relevant research in the field, and no other filters were applied.

Two authors (L.B.C. and L.S·V.) independently reviewed the titles and abstracts of the retrieved citations. Discrepancies were resolved by a third author (D.F.G.). Then, the full texts of the selected citations were assessed.

2.2. Study inclusion and exclusion

We included clinical studies investigating the oral and gut microbial composition in patients diagnosed with AD. Additionally, we included preclinical studies using transgenic mouse models with AD that explored the oral and gut microbial composition. We selected preclinical and clinical studies focusing on investigating relationships between oral or gut microbiota and AD.

Excluded from our analysis were studies involving patients with other neurodegenerative diseases and those that did not employ mammalian animal models in their research.

3. Results and discussion

3.1. Study selection

Initially, 5748 references were found on the three search platforms where our strategy was developed. After screening the documents by title and abstract, 5463 studies were excluded. Subsequently, after accessing the full text of all selected studies, 21 studies not relating to mammals, 32 reviews of other studies, 74 studies not related to AD, and 23 studies not relating to gut and oral microbiota were excluded. In the end, 30 studies were included in the systematic review.

3.2. The gut-microbiota-brain axis in AD

3.2.1. Characteristics of gut-microbiota in AD

Recent research, shown in Table 1, demonstrates that intestinal bacterial composition is altered in AD. In this section, we indicate the most current studies that show the taxonomic bacterial differences

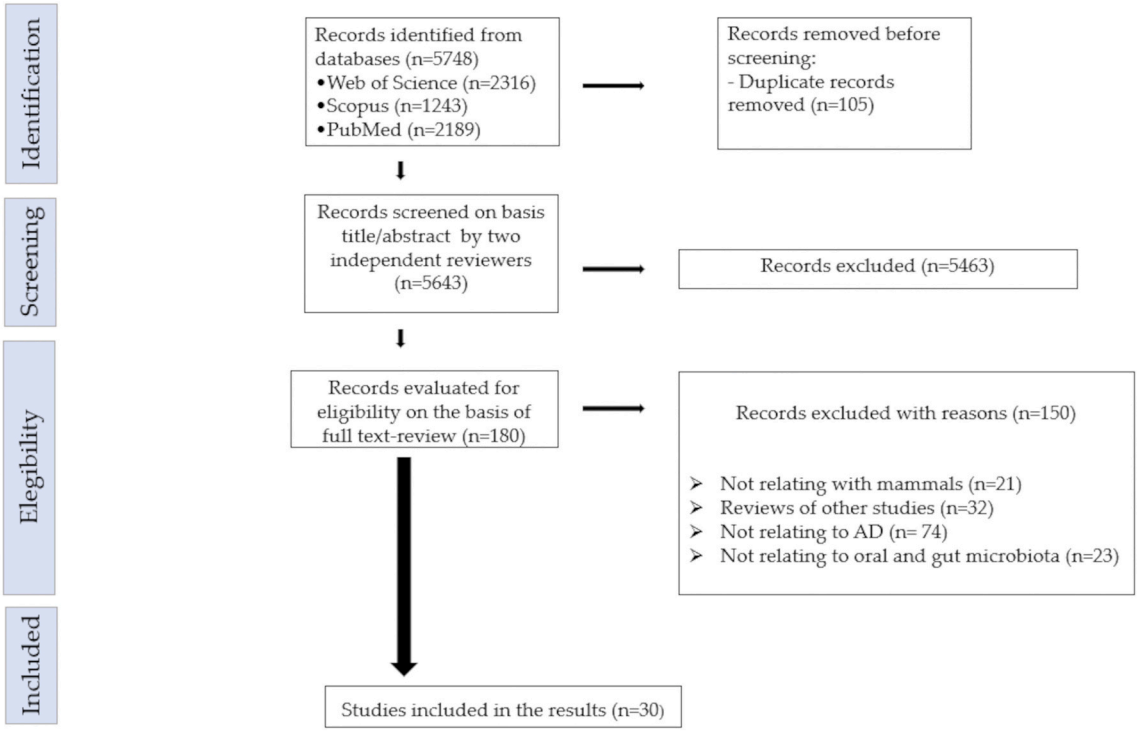

Fig. 1. PRISMA flow chart outlining the search strategy.

Table 1
Characteristics of the gut microbiota in AD.

Ref.	Method	Outcome assessment (Microbiota Analysis)	Results (Bacterial taxonomy)	Conclusions
			Preclinical studies	
[48]	Cases:13 male mice with accelerated senescence (SAMP8). Control: 13 male mice with physiological senescence (SAMR1). Age: 6 months.	-Microbiota characterization: 16S rRNA sequencing in 26 fecal samples followed by metagenomic sequencing.	Decreases: No. of the *Lachnospiraceae* family and genus *Clostridium* and *Blautia*. Increases: No. of the genera *Prevotella* and *Bacteroides*.	There are bacterial taxonomic differences in gut composition between SAMP8 and SAMR1 mice.
[49]	Cases: Young and adult male 5xFAD transgenic mice with a total of five AD-linked mutations. Control: Non-transgenic littermates. Age: 5 and 15 months.	-Microbiota characterization: DNA extraction from colonic flushing followed by quantitative PCR analysis targeting 16S rRNA	In transgenic mice: Decreases: No. of the phylum *Firmicutes*, No. of the genera *Bifidobacteria* and *Lactobacillus*. Increases: No. of the phylum *Bacteroidetes*. There are significant differences between ages in the same genotype.	There are significant alterations in the composition and biodiversity of the gut microbiota of transgenic AD mice compared to non-transgenic mice.
[50]	Cases: 18 APP/PSEN1 transgenic male mice. Control: 18 wild-type littermates. Age: 1, 2, 3, 6 and 9 months.	-Microbiota characterization: Fecal DNA extraction, amplification of 16S rRNA genes, high-throughput sequencing on an Illumina HISeq 1500 squencer	In transgenic mice: Decreases: No. of the phylum *Firmicutes* and *Bifidobacteria* and genus *Bifidobacterium bifidum*. Increases: No. of the genera *Akkermansia*, *Blautia* and *Bacteroides*.	There are variations in bacterial composition at the genus level in the feces of the transgenic mouse model with AD.
[51]	Cases: Transgenic heterozygous female mice (APP/PSEN1). Controls: Wild-type female littermates (C57BL/6). Age: 3, 6 and 24 months.	-Microbiota characterization: Fecal DNA was extracted and the V1-V3 region of the 16S rRNA gene was sequenced by Titanium chemistry (Roche)	Transgenic mice with age: Decreases: No. of the family *Rikenellaceae* and No. of genera *Ruminococcus*, *Oscillospira*. Increases: No. of the genus *Suterella* and No. of the family *Erysilopelotrichaceae*. Stable: No. of the phylum *Bacteriodetes*.	Gut microbiota in mice starts to change after 3 months. By 6 months, there are significant differences in microbiota between transgenic and wild-type mice.
[52]	Cases: 5 CE triple-transgenic mice (3 x Tg-AD) Control: 6 wild- type B6129SF2 mice Age:12–15 months	-Microbiota and mycobiome characterization: Fecal DNA extracted and V4-V6 regions of the 16S rRNA gene was amplify and sequenced by Illumina	Microbiota in transgenic mice: Decreases: No. of the genera *Lachnospiraceae, Ruminococcaceae* and *Turicibacter*. Increases: No. of the genera *Lactobacillus* and *Parasutterella*. Mycobiome in transgenic mice: Increases: No. of the family *Dipodascaceae*.	The composition of the microbiome and mycobiome in 3xTg-AD mice was different compared to WT mice. This supports the hypothesis that various microbial alterations contribute to metabolic proinflammatory imbalances.
			Clinical studies	
[53]	24 patients with AD, 33 patients with other types of dementia and 51 patients without dementia. Age: 85 Location: Massachusetts	-Microbiota characterization: Genomic DNA extracted by PowerMag soil DNA isolation kit and sequenced by NextSeq 500 sequencing system as 2 × 150-bp paired-end reads	In patients with AD: Decreases: No. of the genera *Lachnoclostridium*, *Butyrivibrio* and *Eubacterium*. Increases: No. of the genera *Bacteroides*, *Alistipes*, *Odoribacter* and *Barnesiella*.	Patients with AD exhibit a dysbiotic pattern of gut microbiota compared to those without dementia or with other types of dementia.
[54]	33 patients with AD, 32 patients with MCI (pre-AD stage) and 32 cognitively healthy patients. Age: 50–85 Location: China	-Microbiota characterization: Genomic DNA was extracted by DNA extraction kit (Germany) and 16S rRNA gene was sequenced by Illumina Miseq platform	In patients with MCI, the No. of the phylum *Bacteroidetes* was increased. Patients with AD: Decreases: No. of the phylum *Firmicutes*. Increases: No. of the phylum *Proteobacteria* and the family *Enterobacteriaceae*.	Different bacterial strains, especially *Enterobacteriaceae*, were associated with patients with AD compared to patients with MCI and with cognitively healthy patients.
[55]	34 cognitively normal beta-amyloid negative patients and 32 cognitively normal beta-amyloid-positive patients. Age: 65–70 Location: China	-Microbiota characterization: Genomic DNA was extracted by DNA extraction kit (Germany) and 16S rRNA gene was sequenced by Illumina Miseq platform	In beta-amyloid-positive patients: Decreases: No. of the phylum *Firmicutes*. Increases: No. of the phylum *Bacteroidetes*.	The study provides evidence that gut microbial composition is altered in preclinical AD.
[56]	43 CE patients and 43 cognitively normal patients. Age: 70 Location: China	-Microbiota characterization: genomic DNA was extracted by QIAamp DNA Stool Mini Kit (Qiagen) and 16S rRNA gene was sequenced by Illumina Miseq	In patients with AD: Decreases: No. of the genus *Bacteroides*. Increases: No. of the genera *Ruminococcus,* the family *Lachnospiraceae* and No. of the phylum *Bacteroidetes* and *Proteobacteria*.	The gut microbiota is altered in AD patients and may be involved in their pathology.
[57]	41 CE patients and 43 healthy controls. Age: 68 Location: Nur-sultan (Kazakhstan)	-Microbiota characterization: Genomic DNA was extracted by InviMag Stool DNA kit and 16S rRNA gene was sequenced by Illumina Miseq	In patients with AD: Decreases: No. of the phylum *Actinobacteria*, No. of the family *Lactobacillaceae*, No. of the genus *Bifidobacterium*. Increases: No. of the genera *Akkermansia*, *Niastella*, *Oxalobacter* and *Prevotella*.	The study demonstrated alterations in the gut microbiota of AD patients.

(*continued on next page*)

Table 1 (*continued*)

Ref.	Method	Outcome assessment (Microbiota Analysis)	Results (Bacterial taxonomy)	Conclusions
			Preclinical studies	
[58]	18 patients with AD, 20 patients with MCI and 18 healthy patients. Age: ≥ 60 Location: China	-Microbiota characterization: Genomic DNA was extracted by PowerSoil DNA Isolation Kit and 16S rRNA gene was sequenced by Illumina Miseq	Patients with AD: Decreases: No. of the genera *Lachnospira* and *Bacteroides*. Increases: No. of the genera *Prevotella*, *Ruminiclostridium*.	Patients diagnosed with AD or MCI exhibit intestinal dysbiosis.
[59]	33 patients with AD, 21 with MCI and 116 with SCD. Age: 63 Location: Amsterdam	-Microbiota characterization: 16S rRNA gene was sequenced by Illumina Miseq/ Microseq	Amyloid-positive patients: Increases: No. of the family *Lachnospiraceae*, No. of the genus *Ruminococcus*.	Gut microbiota was associated with amyloid and Tau protein levels.

Abbreviations: AD: Alzheimer's disease; No.: Number; MCI: Mild Cognitive Impairment; SCD: Subjective Cognitive Decline; 16S rRNA: 16S ribosomal RNA.

found in patients and mice with AD in contrast to control cases of cognitively healthy patients.

3.2.1.1. Preclinical studies. The study by Peng et al. [48] focused on comparing the gut bacterial composition and the profile of fecal samples between mice with accelerated cognitive senescence, that is, the mouse model (SAMP8) and control mice (SAMR1) with normal physiological senescence. Analyses showed that the gut microbiota of SAMR1 animals differed from the gut microbiome of SAMP8 mice. The microbiome of AD mice showed a reduced clustering of effective bacterial units. Among the bacterial genera *Prevotella* and *Bacteroides* increased in number, whereas a decrease was shown in *Clostridium* and *Blautia* in SAMP8 mice. Conclusions of the study shows that there are differences in the composition of the intestinal microbiota between the model (SAMP8) and the control group. Moreover, the bacterial taxonomy found was associated with changes in some metabolites related to gut microbiota. Thus, authors indicated that the progression of AD is associated with gut dysbiosis.

Other groups that worked with transgenic mice (APP/PSEN1), carrying mutations in PSEN1 and mutations in APP, studied the bacterial profile in the gut of AD mice [49–51]. Among them, the study by Chen et al. [50] showed that the gut microbiota begins to change at early ages, when amyloid deposition and microglial activation in brain cortex has not yet occurred. Their results showed that APP/PSEN1 elderly mice had an increase in some bacteria expelled in their feces. Among these, *Akkermansia*, *Blautia* and *Bacteroides* stand out. Likewise, other studies showed that there is a different bacterial biodiversity in transgenic mice when compared with control mice, showing significant bacterial taxonomic differences between ages of the same genotype [49,51].

It is worth noting the study by D'Argenio et al. [52], which investigated both the microbiota and mycobiome of transgenic mice with AD. Among their findings, not only was the microbiota altered in transgenic AD mice, but the number of the *Dipodascaceae* family yeast fungi was also increased compared to wild-type control mice. These authors indicated that their results support the idea that several microbial alterations contribute to metabolic and proinflammatory imbalances that consequently enhance the development of pathological conditions.

3.2.1.2. Clinical studies. There is an increasing number of clinical studies trying to underline the link between intestinal microbiota and AD. Haran et al. [53] studied the bacterial taxonomy in individuals with AD, comparing it with two groups: one group in which individuals were diagnosed with another type of dementia and another group without dementia. Their results showed that fecal samples of AD patients had an increase in some bacterial genera such as *Bacteroides* and *Barnesiella* and a decrease in other genera such as *Lachnosclostridium* and *Butyrivibrio*. The authors identified a dysbiosis among AD patients compared to subjects with other types of dementia and those without dementia.

Liu et al. [54], by examination of fecal samples, showed that there was a decrease in microbial diversity in individuals with AD when compared with individuals showing mild cognitive impairment (MCI) and healthy individuals. Fecal samples from AD patients showed a significant bacterial decrease in the phylum *Firmicutes*, while they had an increase in the phylum *Proteobacteria*—especially *Enterobacteriacea* bacteria—compared to fecal samples from healthy individuals. Their results highlighted a significant increase in *Bacteroidetes* during the preclinical stage of AD compared to the group of healthy individuals. Likewise, Sheng et al. [55] indicated that, in early stages of AD, there is an intestinal dysbiosis in which the number of *Bacteroidetes* was increased.

Other studies that compared the bacterial composition of fecal samples from AD individuals with a control group of cognitively healthy individuals stated that a gut dysbiosis exist in AD individuals and may be involved in their pathology [56–58]. Verhaar et al. [59] even put forth an association between gut microbiota and characteristic biomarkers of AD, such as beta-amyloid peptide and hyperphosphorylated Tau protein in cerebrospinal fluid. On the one hand, in fecal samples an increase in *Ruminococcus* and other bacteria in fecal samples was associated with higher probability of amyloid-positive state in cerebrospinal fluid. On the other hand, an increase in bacteria of the *Lachnospiraceae* family was associated with a higher probability of positive Tau protein in cerebrospinal fluid. In conclusion, they stated that gut microbiota was associated with amyloid beta-amyloid peptide and Tau-protein-positive states in cerebrospinal fluid.

It is worth noting that certain bacterial phyla such as *Bacteroidetes* are associated with a negative effect as they are pro-inflammatory bacteria, which can secrete metabolites such as succinate that promotes inflammation, while *Bifidobacterium* and *Actinobacteria* are anti-inflammatory bacterial phyla which can secrete metabolites with an anti-inflammatory response such as SCFAs or neurotransmitters. In pathological conditions, there are alterations in the intestinal microbiota corresponding to a decrease in anti-inflammatory bacterial phyla and an increase in pro-inflammatory bacterial species [60].

3.2.2. The role of gut microbiota in AD pathology

Several studies, listed in Table 2, show the possible interrelationship between microbiota and AD pathology, such as cerebral beta-amyloid deposition and neuroinflammation.

The role of gut dysbiosis was studied in relation to AD pathogenesis. In a preclinical study working with transgenic AD and wild-type mice, a decrease in cerebral amyloid plaques and neurofibrillary tangles was found in control mice. Moreover, metabolites from polyunsaturated fatty acids and oxidating enzymes were found in high concentrations. These might be the outcomes of the activation of inflammation and microglia. The study's conclusions suggest that a dysbiosis in the human microbiome may be a risk factor for AD [61].

Kaur et al. [62], working with AD transgenic mice and wild-type control mice, observed that the AD mice displayed an intestinal dysbiosis. Results showed that AD mice had increased intestinal permeability compared to the control group and also had significantly higher levels of IL-1B and IL-6 compared to the control group.

Basak et al. [63] investigated how exposure to polymicrobial sepsis

Table 2
The role of the gut microbiota in AD.

Ref.	Method	Outcome assessment	Results	Conclusions
			Preclinical studies	
[61]	Cases: 17 $APP^{SWE}/PS1^{AE9}$ transgenic female mice. Control: 48 Female C57BL/6 J wild-type mice. Age: 6–8 weeks.	-Microbiota characterization: DNA extraction from mouse colon, 16S rRNA V4 region amplification and Illumina HiSeq 2500 sequencing	Gut microbiota is significantly different between study and control mice. APP/PS1 mice: lower cognition, higher beta-amyloid peptide.	Exacerbated cognitive symptoms and beta-amyloid deposition in APP/PS1 mice suggest that changes in gut microbiota influence the AD pathology.
[62]	Cases: 30 female APP_{NL-G-F} mice. Control: 30 female C57BL/6 mice, wild-type. Age: 6–8 months.	-Microbiota characterization: Fecal samples were collected after 8 weeks of probiotic treatment and sent for 16S rRNA sequencing.	Intestinal dysbiosis in the mice with AD: -Increased intestinal permeability. -Increased systemic inflammation. -Probiotic supplementation decreased inflammation.	Intestinal dysbiosis led to an increased in intestinal permeability and a systemic inflammation state. Supplementation exerted a beneficial effect.
[63]	Cases: APP/PSEN1 transgenic mice. Cecal ligation and puncture performed to induce microbial sepsis. Age: 2 months.	-Brain sample collection, histological staining and image acquisition. -Microbiota characterization: Genomic DNA was extracted from various tissue samples using TRIzol reagent. The V4 region of the 16S rRNA gene was sequenced using Illumina MiSeq.	Mice surviving microbial sepsis: -Hippocampal amyloid fibrillar load was increased. -Total astrocyte levels were increased.	Experimental sepsis may aggravate inflammation-related hippocampal beta-amyloid burden.
[64]	Cases: Male C57BL/6 J mice: Injected with beta-amyloid- 42 into the lateral ventricle. Age: 10 weeks.	-Microbiota characterization: DNA was extracted, V3-V4 region of the 16S rDNA was amplified via PCR. Quantification and sequencing were performed on Illumina platform.	Injection of beta-amyloid induced: -Neuronal damage and cognitive impairment. -Alteration in gut microbiota after 4 weeks. -Increased levels of pro-inflammatory factors.	The authors suggest that beta-amyloid peptide in CNS induces gut dysbiosis and accelerates amyloidogenesis.
[65]	Cases: Transgenic AD mouse ($ADLP^{APT}$). Control: Healthy wild-type mice. Age: 8 months.	-Microbiota characterization: Fecal metagenomic DNA was extracted and 16S rRNA gene hypervariable regions were sequenced using 454 pyrosequencing GS FLX Titanium (Roche) and Illumina MiSeq sequencing.	The composition of the microbiota of ADLP mice differed from the composition of healthy mice. ADLP mice: -Loss of epithelial barrier integrity. -Systemic inflammation. Transfer of feces from healthy mice to ADLP mice: -Improved cognitive impairment. -Relieved intestinal barrier integrity and amyloid plaque burden.	Restoring gut bacterial homeostasis may have beneficial effects in the treatment of AD.
[66]	Cases: AD Tg mice (5xFAD) Control: WT mice	-Microbiota characterization: Via 16S rRNA gene sequencing, measuring short-chain fatty acid amounts and employing behavioural test, mass spectrometry	Co-housing between WT mice resulted in AD-associated gut microbiota dysbiosis, Tau phosphorylation and cognitive impairment in WT mice.	The authors suggest a potencial link between the transmission of AD-associated microbiota dysbiosis and development of cognitive impairment.
[67]	Cases: 8 Male 5xFAD mice. Control: 8 Male wild-type C57BL/6 mice. Age: 8 weeks.	-Microbiota characterization: Fecal DNA was extracted and 16S rRNA genes were amplified using V3-V4 primers and sequencing was conducted on Miseq platform Illumina	Transplantation of altered microbiota from AD mice into healthy mice: -Decreased hippocampal neurogenesis. -Increased pro-inflammatory cytokines in the colon and blood.	The microbiota of AD mice may cause inflammation in the colon and cognitive impairment. Dysbiosis may play a critical role in several mechanisms underlying AD.
[50]	Cases: APP/PSEN1 transgenic male mice. Control: Wild-type littermates. Age: 1, 2, 3, 6 and 9 months.	-Microbiota characterization: Fecal DNA extraction, amplification of 16S rRNA genes, high-throughput sequencing on an Illumina HISeq 1500 squencer	At advanced ages, transgenic mice with AD had abundance of *Escherichia*, *Shigella* and *Desulfovibrio,* bacteria associated with an inflammatory profile. This also coincided with an abundant microglia burden in brain amyloid deposition.	The results suggest dysbiosis precedes the development of pathological features of AD, including amyloidosis and neuroinflammation.
[68]	Cases: APP/PSEN1 transgenic mice. Age: 1, 2 and 3 months.	-Amyloid Plaque measurement by image analysis. -Mouse behaviours test: Barnes Maze test -Fatty Acid Analysis by GC/MS-based SCFA Analysis -Protein Activity Assays	Supplementation of SCFAs in AD mice increased the burden of brain beta-amyloid plaques.	SCFAs are critical mediators in the microbiota–gut–brain axis that promotes beta-amyloid accumulation, possibly by modulating the microglial phenotype.
			Clinical studies	
[69]	Cases: 64 patients with neurodegenerative diseases such as AD. Control: 64 patients without neurodegenerative disease. Aged: 66–75 Location: Rome (Italy)	- NOx2 was measured and assessed in serum using an ELISA method -Blood levels of LPS measured using ELISA kits.	Patients with neurodegenerative disease had high NOX2 values.	Patients with neurodegenerative diseases, such as AD, exhibit high activation of NOX2 which may be involved in the process of neuroinflammation.
[70]	Cases: 89 people with cognitive performance ranging from normal to dementia, measured LPSs and SCFAs levels in blood. Aged: 50–85 Location: Italy	-Brain amyloidosis assessed by florbetapir amyloid PET imaging -Blood levels of LPS measured using ELISA -SCFAs were measured by mass spectrometry	Brain amyloid burden was associated with the level of LPSs, acetate and valerate, as well as with pro-inflammatory cytokines in blood and endothelial dysfunction. It was not associated with anti-inflammatory cytokine IL-10 or butyrate.	The authors suggest that there is an association between gut microbiota-related products and systemic inflammation with cerebral amyloidosis via endothelial dysfunction. SCFAs and LPSs represent pathophysiological mechanisms linking gut microbiota and AD.

(*continued on next page*)

Table 2 (*continued*)

Ref.	Method	Outcome assessment	Results	Conclusions
			Preclinical studies	
[71]	Cases: Serum samples were collected from 1562 patients with neuroimaging characteristic of AD. Location: USA	-Bile acids concentrations were measured using liquid chromatography tandem mass spectrometry -Neuroimaging processing by florbetapir PET scans and CSF biomarkers	Out of the 23 bile acids studied, 3 acids were found to be associated with beta-amyloid in cerebrospinal fluid and three acids were associated with hyperphosphorylated tau protein.	The authors suggest that serum bile acid metabolites are related to AD biomarkers.

Abbreviations: AD: Alzheimer's disease; APP/PSEN1: Mutations in amyloid precursor protein and presenilin 1; LPS: Lipopolysaccharides; SCFAs: Short-chain fatty acids; PET: Positron Emission Tomography; ELISA: Enzyme-linked immunosorbent assay; CSF: Cerebrospinal Fluid.

influences brain deposition of beta-amyloid peptide in a preclinical study. They used transgenic mice (APP/PSEN1) carrying the APP mutation and the PSEN1 mutation and mice for the control group (C57BL6). All of them underwent polymicrobial sepsis. The results showed that mice surviving the experimental microbial sepsis had a significantly higher hippocampal fibrillary amyloid load compared to the control group. In the long term, sepsis also caused brain neuroinflammation in APP/PSEN1 mice, with elevated astrocyte activation. They also observed that there was a significant dysbiosis in the gut microbiota of the transgenic mice after sepsis, with an increase in the bacterial phylum of *Bacteroidetes* and *Proteobacteria* and a decrease in *Firmicutes*. Thus, the authors suggested that sepsis may modify the gut microbiota toward a pro-amyloidogenic and neuroinflammatory state.

Nevertheless, Quian et al. [64] in their preclinical study stated that CNS inoculation of peptide-beta amyloid-42 may induce gut dysbiosis, trigger altered gut structure and accelerate amyloidogenic pathways. This conclusion comes from the fact that injection of beta-amyloid-42 into the cerebral lateral ventricle induced cognitive impairment and neuronal damage and also altered gut microbiota at 1 month in mice.

Kim et al. [65] observed that the gut microbiota of transgenic mice with AD was altered and distinguished from the microbiota of healthy wild-type mice. To clarify the implication of the gut dysbiosis occurring in the transgenic mice on AD pathology, the researchers transferred fecal samples from healthy mice to the AD transgenic mice on a daily basis. They observed that continued exposure to a healthy gut microbiota could improve the cognitive status of the mice with AD. In addition, they observed that there was a hippocampal decrease in beta-amyloid load and hyperphosphorylated Tau protein aggregates. Nevertheless, Zhang et al. [66], investigated the dysbiosis of the gut microbiota associated with AD and its potential transmission from AD mice (ADTg) to wild-type mice (WT), as well as from AD patients to their partners. Their results revealed that WT mice that received fecal microbiota from ADTg mice developed cognitive impairment. This suggests that active ingestion (cohabitation) of feces from ADTg mice can induce cognitive impairment in WT mice. Furthermore, a similar pattern was observed in AD patients and a control group that did not have AD and lived in the same household. Both groups had a similar intestinal bacterial taxonomy. This study provides evidence supporting the potential transmission of Alzheimer's disease-associated gut microbiota from AD patients or AD transgenic mice to unaffected controls cohabiting with them.

In a similar preclinical study, altered fecal microbiota derived from transgenic mouse models with AD (5xFAD) was transplanted to normal mice (C57BL/6). It was observed that there was a decrease in neurogenesis and an increase in hippocampal neuroinflammation, leading to cognitive impairment. The transplanted mice had high levels of some pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1B, in the colon and plasma compared to the control mice group. The mouse models with AD even had significantly increased levels of TNF-α and IL-1B in the hippocampus. Following these results, the findings indicated that intestinal dysbiosis is linked to the pathogenesis of AD, such as neuroinflammation or decreased neurogenesis [67].

Some researchers observed that the intestinal bacterial composition of transgenic mice with AD-like pathology presented bacterial taxa related to inflammation, such as *Escherichia*, *Shigella*, *Akkermansia*, *Desulfovibrio* and *Blautia*, which occurred together with abundant microglial accumulation in areas of cerebral beta-amyloid deposition [50].

Despite the observed interaction between gut microbiota and AD pathogenesis, the underlying mechanisms were elusive. Colombo et al. [68] in a preclinical study identified that SCFAs, which come from bacterial fermentation of fiber, acted as bacterial metabolites that promoted brain beta-amyloid deposition. The amyloid-positive mice (APPPS1) had high levels of SCFAs concentrations in their blood compared to the concentrations of mice in the control group. To study the relationship between these metabolites and beta-amyloid peptide burden, the authors administered a combination of three types of SCFAs (acetate, propionate and butyrate) to the group of transgenic mice. The authors showed that SCFAs supplementation increased the number of cerebral beta-amyloid plaques almost twofold, they even observed that this supplementation affected the appearance of new amyloid plaques more than the growth of existing plaques and functional alterations of microglia caused by SCFAs.

Loffredo et al. [69] focused on the role of LPSs, products derived from intestinal Gram-negative bacteria, in neurodegenerative diseases such as AD. The role of oxidative stress, particularly reactive oxygen species derived from NADPH oxidase 2 (NOX2), are important in cell apoptosis and in mediating CNS inflammatory responses. Through oxidative stress, generated by NOX2, the proliferation and differentiation of immune T cells that may participate in inflammatory and neurodegenerative processes is promoted. In order to better understand the possible cause of NOX2 activation, the authors analyzed the intestinal microbiota by means of a clinical study. It showed that NOX2 activation is related to bacterial LPSs obtained by blood samples. The authors showed evidence that patients with neurodegenerative diseases such as AD show high NOX2 activation and suggest that the gut microbiota dysbiosis is a potential source of oxidative stress.

Marizonni et al. [70] also investigated the association of AD amyloid pathology with SCFAs such as acetate, valerate and butyrate and LPSs. The results of the clinical study showed that high blood levels of LPSs were associated with increased amyloid pathology in the frontal cortex, posterior cortex, cingulate cortex and a part of the parietal area, the precuneus. Among the SCFAs, acetate and valerate were associated with cerebral amyloid deposition, not so much with butyrate, which showed a negative association. In addition, they evaluated the blood level of proinflammatory cytokine concentration, indicating that some inflammatory cytokines such as IL-1B, NLRP3, IL-6 and CXCL2 were associated with high levels of brain amyloid load, mostly in the posterior cingulate cortex.

Serum levels of some bile acids, which are end products of cholesterol metabolism produced by human co-metabolism and by the intestinal microbiota, were also analyzed. Bile acids are often altered in MCI and AD. The researchers analyzed serum concentrations of primary conjugated bile acids and secondary conjugated bile acids; the latter produced by intestinal bacteria in adults with early-stage AD. They observed that altered bile acids produced by bacteria were associated with AD biomarkers, including beta-amyloid peptide, hyperphosphorylated Tau protein, brain glucose metabolism, and structural atrophy. This study showed an association between gut microbiota

markers and liver function with AD biomarkers [71].

3.2.3. NLRP3 and its role in AD

To better understand the relationship between gut microbiota and the increased neuroinflammation in AD, some authors investigated the role of NLRP3 inflammasome in AD. Two studies showing such a relationship between NLRP3 expression and AD are shown in Table 3.

Shen et al. [72] worked with three groups of APP/PSEN1 transgenic mice. In one group, intestinal microbiota from healthy patients was transplanted via fecal samples to improve the microbiota they had, another group of mice received minocycline to inactivate and improve intestinal bacteria and another group were not treated with antibiotics and were not transplanted. The results indicated that the levels of NLRP3 inflammasome proteins in the intestine were significantly increased, as were the levels of intestinal inflammation and the levels of blood inflammatory factors in the APP/PSEN1 mice that did not receive any treatment or healthy intestinal microbiota. Whereas, the mice treated with minocycline and transplanted with healthy gut microbiota showed an improvement in cognitive ability and a decrease in the level of microglial activation, compared to the study group. Thus, a healthy gut microbiota would improve cognitive ability and neuroinflammation in mice suffering from AD. Their findings indicated that the gut microbiota in AD patients can promote the intestinal inflammatory response through the NLRP3 inflammasome, achieving hippocampal microglial activation.

Shukla et al. [49] through a preclinical study investigated the relationship between gut dysbiosis and neuroinflammation in AD progression. They showed that altered gut microbiota in transgenic mice suffering from AD was accompanied by increased protein expression of NLRP3 in colon tissue compared to control group mice without AD. Also, the authors analyzed the level of NLRP3 expression in the hippocampus and observed that the levels were significantly increased in the transgenic mice compared to the control group. The NLRP3 inflammasome located in microglia and astrocytes triggers a production of proinflammatory cytokines such as IL-1, so that NLRP3 expression in astrocytes and microglia of transgenic mice activates an inflammatory response that can lead to AD pathology and memory loss.

3.3. The oral-microbiota-brain axis

3.3.1. Characteristics of oral-microbiota in AD

Recently, research on oral microbiota has attracted significant attention since toxic proteases, called gingipains, from the bacteria *Porphyromonas gingivalis* have been found in brain tissue AD patients [73].

Several studies have shown alterations in the oral microbiota of AD patients (Table 4). The composition of oral microbiome was different between the group of patients with AD and the cognitively unimpaired group [74,75]. The authors Chen et al. [76] studied the composition of the oral microbiota and the gut microbiota of individuals with mild and moderate AD compared to data from a control group of individuals with normal cognition. In their results they showed that there are significant alterations in the oral microbiota among the three groups of individuals. The phylum *Firmicutes* with its corresponding family *Veillonellaceae* and *Streptococcaceae* and the phylum *Fusobacteria*, to which the family *Leptotrichiaceae* belongs, were found to be more abundant in individuals with mild and moderate AD than in the control group of individuals, with these bacterial strains being significantly more abundant in the group of individuals with moderate AD. Taxa of the phylum *Proteobacteria*, *Verrucomicrobia* and *Actinobacteria* were significantly less abundant in the moderate AD group compared to the control group and the group of individuals with mild AD. Thus, they concluded that the compositions of the oral microbiota differed when compared between different stages of AD. Furthermore, Wu et al. [75] conducted a study in which they observed that individuals with AD had a lower diversity of oral microbiota indicating a dysbiosis in the oral cavity of the individuals. Also, the authors observed that individuals with AD had a significantly higher number of missing teeth and a higher concentration of dental plaque.

3.3.2. The role of oral microbiota in AD pathology: Periodontitis

The relationship between the composition of oral microbiota and some neurodegenerative diseases, such as AD, remains unclear [74]. However, some studies show a relationship between PD and AD (Table 5).

Results from a preclinical work showed that *Porphyromonas gingivalis* infection caused an increase in IL-1B production followed by an intracellular accumulation of beta-amyloid peptide in liver macrophages of mice infected with the bacteria. Thus, Nie et al. [77] came closer to understanding the possible involvement of PD in the pathological progression of AD. In a similar study, Illievski et al. [78] showed that oral administration of *Porphyromonas gingivalis* in wild-type C57BL/6 mice resulted in neuroinflammation, neurodegeneration, microgliosis, astrogliosis and senile plaque formation by beta-amyloid peptide, pathological signs of AD. Their results suggest that chronic oral infection with the bacteria *Porphyromonas gingivalis* may promote the development of neuropathology consistent with AD in humans.

More specifically, Lu et al. [79] demonstrated that PD may be involved in the pathogenesis of AD. They conducted their study by collecting salivary samples from individuals with periodontitis and from

Table 3
NLRP3 and its role in AD.

Ref.	Method	Outcome assessment	Results	Conclusions
[72]	Cases: 10 transgenic mice with AD (APP/PSEN1). Control: Wild-type mice (C56BL/6). Transplanted fecal samples: Include fecal samples from cognitively healthy individuals and from individuals with AD.	-Neurobehavioral testing: Morris water maze test -Immunofluorescence and Tissue Cytology for detect NLRP3 -Immunohistochemistry was performed in mouse hippocampus -Western Blot to determine expression of inflammation-related proteins	Transplantation of altered microbiota from AD patients into C56BL/6 mice: -Increased intestinal expression of NLRP3. Transplantation of healthy human microbiota into APP/PSEN1 mice: -Upregulated NLRP3 expression, and improved cognitive ability	Gut microbiota in AD patients can induce activation of the NLRP3 inflammasome in the mouse intestine, leading to the release of inflammatory factors.
[49]	Cases: Young and adult male 5xFAD transgenic mice with a total of five AD-linked mutations. Control: Non-transgenic littermates. Age: 5 and 15 months.	-DNA extraction from colonic flushing followed by quantitative -PCR analysis targeting 16S rRNA	The altered microbiota of AD transgenic mice correlates with abnormally elevated intestinal NLRP3 expression. Increased inflammasome correlates with increased brain astrocytes and microglia, along with brain IL-1B production.	The authors indicated that intestinal NLRP3 may be an important trigger for the subsequent activation of inflammatory mediators.

Abbreviations: AD: Alzheimer's disease; NLRP3: Nucleotide-binding domain, leucine-rich repeat protein; APP: Amyloid precursor protein; PSEN1: Presenilin 1; 16SrRNA: 16S ribosomal RNA; IL-1β: Interleukin-1beta.

Table 4
Characteristics of oral-microbiota in AD.

Ref.	Method	Outcome assessment (Analysis microbiota)	Results	Conclusions
[74]	Cases: 50 patients with AD with PD Control: 14 cognitively unimpaired with PD Location: Yangsan (South Korea)	-Microbiota characterization: PCR amplification of 16S rRNA gene V3-V4 region was performed and sequenced with HiSeq Illumina	The level of oral microbiota in patients with AD was higher than in cognitively unimpaired patients with PD. The bacterial species *Prevotella* was more prevalent in subgingival samples from the AD group.	The composition of oral microbiome was different between the AD and the cognitively unimpaired group.
[75]	Cases: 17 patients with AD Control: 18 normal elderly individuals Aged: 65–78 Location: Taiwan	-Microbiota characterization:16S rDNA sequenced was amplified and sequenced using Pac Bio technology	Patients with AD: Increased no. *Lactobacillales, Streptococcaceae,* and *Firmicutes/Bacteroidetes* Decreased no. *Fusobacterium.*	Patients with AD had lower diversity of the oral microbiota and had significantly more missing teeth and higher dental plaque.
[76]	172 individuals classified: Normal cognition: 40 Mild AD: 43 Moderate AD: 89 Aged:70–82 Location: Fujian (China)	-Microbiota characterization: PCR was performed to amplify V3-V4 hypervariable regions of bacterial 16S rRNA gene and was sequencing by Illumina MiSeq system	There was a progressive increase from normal cognition to mild AD and to moderate AD groups in *Firmicutes* and *Fusobacteria* abundances. These taxa were significantly higher in moderate AD group. There was a progressive decrease from normal cognition to mild AD and to moderate AD groups in *Proteobacteria* abundances. These taxa were significantly less abundant in moderate AD group.	The compositions of the oral microbiota differed when compared between different stages of AD.

Abbreviations: AD: Alzheimer's disease; PD: Periodontal disease; 16S rDNA: 16S ribosomal DNA.

Table 5
The role of oral microbiota in AD pathology: Periodontitis.

Ref.	Method	Outcome assessment	Results	Conclusions
[77]	Cases: 10 female mice C57BL/6 J were infected with *P. gingivalis* Control: 10 female mice C57BL/6 J without *P. gingivalis* Age: 12 weeks	-mRNA isolated from liver tissues of mice after *P. gingivalis* infection and subjected to PCR -Phagocytic activity assay -Immunofluorescence imaging	There was an increased expression of IL-1β and beta-amyloid in macrophages of *P.gingivalis*-infected mice.	Chronic systemic *P. gingivalis* infection induces the production of beta- amyloid peptide in inflammatory macrophages.
[78]	Cases: 10 wild type C57BL/6 with oral application of Pg/gingipain Control: 10 wild type C57BL/6 received vehicle alone Age: 8 weeks	IF and confocal microscopy was performed for the detection of beta-amyloid peptide, intact neurons, microglia, astrocytes, degrading neurons, proinflammatory cytokines and *P. gingivalis*	It was observed that there was more *P. gingivalis,* inflammation, amyloid peptide, Tau protein, microgliosis, astrogliosis, and fewer intact neuronal cells in the hippocampus of experimental group than in the control group.	Low-grade chronic periodontal pathogen infection can result in the development of neuropathology that is consistent with that of AD.
[79]	Cases: 27 patients with periodontitis Control: 26 healthy controls Age: 31–32 Location: China Animal model: 30 $APP^{SWE}/PS1^{AE9}$ transgenic mice Age: 4 months	Salivary microbiota from patients with periodontitis and healthy controls was used to gavage transgenic AD mice. Saliva samples was assessed using 16S rRNA sequencing -Conducted behavioural tests to evaluate anxiety and cognitive impairment	-Periodontitis- related salivary microbiota in $APP^{SWE}/PS1^{AE9}$ transgenic mice: -Exacerbates the anxiety and cognitive impairment - Increases beta-amyloid accumulation and neuroinflammation -Induces gut microbial dysbiosis	Periodontitis might participate in the pathogenesis of AD by swallowing salivary microbiota, suggesting the significance of oral examination and treatment in the prevention of AD.

Abbreviations: AD: Alzheimer's disease; *P.gingivalis*: *Porphyromonas gingivalis*; IF: Immunofluorescence microscopy; PCR: Polymerase Chain Reaction; 16S rRNA: 16S ribosomal RNA.

healthy individuals. For two months, the salivary microbiota was fed to transgenic mice with AD. Their results showed that the mice exhibited faster cognitive decline, increased brain beta-amyloid concentration and increased neuroinflammation, suggesting that dysbiosis in the oral microbiota may aggravate the pathogenesis of AD. This study showed the role of PD in the progression of AD pathology.

3.4. The role of the microbiota as a therapy in AD

Probiotics are live microorganisms that can improve the micro-ecological balance of the host and play a beneficial role. The latest research (Table 6) shows that the microbiota may also have therapeutic roles in AD.

While probiotics are live microorganisms, prebiotics are oligosaccharide and polysaccharide structures that can beneficially modulate the gut microbiome by improve the growth and function of gut microbes

Table 6
The role of the microbiota as a therapy in AD.

Ref.	Method	Outcome assessment	Results	Conclusions
[81]	Cases: APP/PS1 mice: AD group and AD+Bi group Control: Wild Type mice: WT group and WT+ Bi group Age: 4–10 months	Treatment with *Bifidobacteria* lasted for 6 months. Mice were prepared for: -Immunohistochemistry -Immunofluorescence -Thioflavin S staining -Western blotting -PCR -ELISA quantitative assay.	The level of insoluble peptide beta-amyloid in the hippocampus and cortex of AD+Bi mice was decreased compared with AD mice. *Bifidobacteria* inhibited microglial activation and reduced IL-1β, TNF-α, IL-4, IL-6 and INF-γ	Treatment with *Bifidobacteria* can suppress beta-amyloid accumulation and neuroinflammation in APP/PS1 mice.
[82]	Cases: Male adult C57BL/6 J with amyloid beta intrahippocampal injection Control: Male adult C57BL/6 J Age: 6 weeks	-Microbiota characterization: Microbial genomic DNA was extracted from fecal samples, and V3-V4 region of bacterial 16S rRNA was amplificated and sequenced on a MiSeq platform Illumina. -Behavioural tests	Environmental enrichment combined with treatment with *Bifidobacterium breve* significantly alleviated amyloid peptide, restored gut microbiota dysbiosis, reversed microbial metabolites, and inhibited neuroinflammation.	A combination of dietary microbiome-based approaches and lifestyle interventions can be an intervention strategy to prevent cognitive decline.
[62]	Cases: 30 female APP_{NL-G-F} mice. Control: 30 female C57BL/6 mice, wild-type. Age: 6–8 months.	-Microbiota characterization: Fecal samples were collected after 8 weeks of probiotic treatment and sent for 16S rRNA sequencing.	Probiotic supplementation decreased inflammatory and increases tight junction intestinal proteins. It had no effect on beta-amyloid accumulation, cytokines or gliosis.	Dietary manipulation through probiotic intervention appears to be an attractive means of attenuating the intestinal aspect of AD.
[83]	Cases: 20 APP^{SWE}/PS1dE9 transgenic AD model mice (APP/PS1) Control: C57BL/6 (WT) mice Age:6 months	-APP/PS1 transgenic were treated intragastrically with CB for 4 weeks -Microbiota characterization: DNA was extracted and V3-V4 region of the 16S rRNA gene was amplified using an Illumina MiSeq platform -Behavioural tests -ELISA assay	*Clostridium butyricum* treatment prevents cognitive impairment, beta-amyloid deposits, microglia activation	*Clostridium butyricum* treatment could attenuate microglia-mediated neuroinflammation via regulating the microbiota-gut-brain-axis
[84]	Cases: Male 5xFAD transgenic mice Control: Male C57BL/6 mice Age: 4,18 months and 6 weeks	-Behavioural tests -Isolation and culture macrophages: Macrophages are isolated and treated with LPS -Immunoblotting and ELISA -Immunohistochemical and Immunofluorescence Assay -Microbiota characterization: Bacterial genomic DNA and 16S rRNA gene sequencing	Oral administration of *Lactobacillus mucosae* and *Bifidobacterium longum* decreased cognitive impairment-like-behaviours, hippocampal amyloid-beta, TNF-α and IL-1β. It also reduced TNF-α and IL-1β in colon.	Bacteria and their product LPS may be closely connected with occurrence of cognitive impairment and neuroinflammation. Some probiotics like *Lactobacillus mucosae* and *Bifidobacterium longum* can additively alleviate cognitive impairment and neuroinflammation.

Abbreviations: AD: Alzheimer's disease; PCR: Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunosorbent Assay; IL-1β; Interleukin- 1 beta; TNF-α: Tumor Necrosis Factor-alpha; IL-4: Interleukin- 4; IL-6: Interleukin- 6; INF-γ: Interferon-gamma; 16SrRNA: 16 ribosomal RNA; LPS: Lipopolysaccharides.

[80].

Wu et al. [81] worked on a preclinical study showing that some bacteria such as *Bifidobacteria* can play a beneficial role in AD pathology. They worked with four groups of mice: a wild-type control group, a control group given *Bifidobacteria*, a group of APP/PSEN1 mice and a group of APP/PSEN1 mice given *Bifidobacteria*. They examined how *Bifidobacteria* affected amyloid plaque formation in the brain, and the results showed that amyloid deposition in the hippocampus and cerebral cortex decreased in AD transgenic mice given *Bifidobacteria* compared to AD mice. They also studied how these bacteria affect neuroinflammation and observed that some proinflammatory factors such as TNF-α, IL-1B, IL-4 and IL-6 were increased in AD mice compared to control mice. However, in mice that were treated with *Bifidobacteria*, the level of these factors was reduced compared to AD mice. Therefore, they concluded that probiotics with *Bifidobacteria* is a potential therapeutic weapon as it can suppress beta-amyloid accumulation and neuroinflammation in AD mice.

Zhu et al. [82] also studied the effect of the probiotic *Bifidobacterium breve* on AD pathology. Mice with AD that were treated with the probiotic of some strains of *Bifidobacterium breve* showed significant improvements in behavior and cognition as well as relieved neuroinflammation. Their findings indicated that this bacterium alleviates cognitive impairment and delays the progression of pathology in AD in mice.

Similarly, in a preclinical study mentioned above, Kaur et al. [62] also studied the possible benefit of probiotics in AD. They worked with transgenic mice containing mutations in APP, thus suffering from AD, and with a control group of wild-type mice. A set of mice from both groups were administered a probiotic complex consisting of: *Lactobacillus plantarum*, *Bifidobacterium infantis, Lactobacillus delbrueckii*, *Lactobacillus acidophilus Bulgaricus*, *Lactobacillus paracasei*, *Bifidobacterium breve*, *Bifidobacterium longum* and *Streptococcus salivarius*. Probiotic supplementation produced a decrease in inflammatory protein level and improved intestinal dysfunction, since probiotics decreased intestinal inflammation and improved intestinal leakiness. However, they did not observe a significant reduction in brain amyloid burden.

Sun et al. [83] studied the probiotic effect of *Clostridium butyricum* bacteria in transgenic mice (APP/PSEN1). They observed that supplementation with this bacterium showed improvements in the cognitive capacity of transgenic mice, decreased neurodegeneration and microglia-mediated neuroinflammation. Thus, they concluded that supplementation with *Clostridium butyricum* may be beneficial in inhibiting neuroinflammation in AD.

Some anti-inflammatory probiotics like *Lactobacillus mucosae* and *Bifidobacterium longum*, which suppress the expression of TNF-α in LPS-stimulated macrophages, may alleviate certain neuropsychiatric disorders such as AD. Ma et al. [84], in their study, observed that the administration of both *Lactobacillus mucosae* and *Bifidobacterium longum* to transgenic mice with AD (5XFAD) reduced cognitive impairment, hippocampal amyloid peptide accumulation, and hippocampal IL-1β expression. Furthermore, it decreased IL-1β and TNF-α expression in the colon and positively modulated the gut microbiota, reducing LPS levels in feces and blood, as well as the populations of intestinal *Proteobacteria* and *Verrucomicrobia,* which are associated with high levels of TNF-α in the hippocampus. This suggested that LPS and certain gut bacteria are related to the onset of cognitive impairment and neuroinflammation, and some probiotics like *Lactobacillus mucosae* and *Bifidobacterium longum* may alleviate these symptoms.

Therefore, a future therapeutic strategy such as modulation of intestinal bacterial populations by probiotics and prebiotics could ameliorate symptoms of AD or decelerate the disease progress [80,85]. Likewise, environmental factors such as diet act as modulators in the composition of the gut microbiota [86] whereby diet has regulatory effects on physiological functions and the CNS in AD by altering the gut microbiota and its metabolites [87].

Also, it should be essential to focus on the relationship between AD and PD. Thus, effective treatment of the latter and adequate oral care could represent a therapeutic strategy for the management of AD [24,28].

Therefore, as future recommendations and healthy practices to delay the onset of cognitive decline in AD patients, further evaluation of the therapeutic benefits of controlled microbiota modification in AD through probiotic supplementation or diets designed for this pathology could be carried out. Also, healthcare professionals should insist in individuals with AD and their relatives on cleanliness and oral care of the individuals.

4. Conclusions

Based on the various studies reviewed regarding intestinal microbiota, oral microbiota and AD, this review suggests a clear relationship between the composition of intestinal and oral bacteria and AD. Bacterial dysbiosis appears to be closely related to AD pathology. Thus, in line with the objective outlined in this review we conclude that the gut microbiota is linked to the neuroinflammation characteristic of AD. However, the exact mechanisms underlying this relationship remain unclear. What does appear evident is the bidirectional connection between brain beta-amyloid peptide accumulation and dysbiosis of the gut microbiota. It is worth noting that a balanced oral microbiota can act as a barrier to pathogens, and research has shown that infectious agents such as *Porphyromonas gingivalis* can spread amyloid peptide plaques from peripheral organs such as liver. Liver macrophages have the potential to transport beta-amyloid to the brain, thereby increasing neuroinflammation and exacerbating the progression of AD pathology.

This highlights the need for further research, both basic and clinical, to gain a deeper understanding of the role of the microbiome and derived metabolites in the AD pathogenesis, particularly in relation to the microbiota-gut-brain axis.

Finally, it is important to emphasize that the microbiota composition in AD patients has been determined to be characteristic, leading to an increased systemic pro-inflammatory state and subsequent cognitive impairment.

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