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The relationship of chronic neuronal inflammation (neuroinflammation) to neurodegeneration is exemplified by Alzheimer's Disease and alternative therapeutic approaches: Narrative review

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ABSTRACT

Neuroinflammation is a crucial factor in the development of neurodegenerative disorders, particularly Alzheimer's Disease (AD), the focus of this review. AD is the most common cause of dementia and age-related cognitive impairment. The existing hypotheses do not fully elucidate the pathogenesis of AD. Neuroinflammation may prove to be a critical pathogenetic component of AD and an important therapeutic target. The mechanisms underlying neuroinflammation include dysregulation of the microbiota and dysfunction of the gut-brain axis, blood-brain barrier pathology, microglia cell activation, and oxidative stress. The presence of elevated levels of inflammatory biomarkers, including IL-1β (interleukin 1β), IL-6 (interleukin 6), and TNF-α (tumor necrosis factor- α), has been demonstrated in AD cases in comparison to healthy subjects. Furthermore, imaging studies lend support to the inflammatory theory of neurodegenerative diseases. The following section will analyze the various therapeutic strategies that have been suggested for the treatment of AD. Further research into the inflammatory processes in neurodegenerative diseases is essential to develop effective therapeutic strategies for patients.

Keywords: Neuroinflammation, neuronal inflammation, neurodegeneration, Alzheimer's disease

1. INTRODUCTION

The progressive death of nerve cells is characteristic of neurodegenerative diseases. From a clinical perspective, these conditions are distinguished by a reduction in motor and cognitive abilities. The most prevalent disease within this category is Alzheimer's disease, which has been the primary focus of this review. Other diseases in this group include Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, Alexander's disease, spinal muscular atrophy, and others. In Poland in 2019, the Institute for Health Metrics and Evaluation reported that 585,000 individuals (1.5% of the population) were affected by Alzheimer's disease and related disorders. In the United States, 6.7 million Americans over the age of 65 are affected, and it is estimated that this number could rise to 13.8 million by the year 2060.

The incidence of neurodegenerative diseases rises with age. At present, the precise etiology of these conditions remains unclear. In recent years, the inflammatory theory of neurodegenerative diseases has gained considerable support within the scientific community. The hypothesis is that a chronic, low-grade inflammatory process within neurons may play a significant role in the etiology of neurodegenerative diseases (Zhang et al., 2023). Furthermore, subsequent sections of the chapter will examine the influence of compounds that mitigate the severity of inflammatory processes within the body, which may potentially diminish the probability of Alzheimer's disease or impede its progression.

2. METHODOLOGY

The following paper presents a comprehensive analysis of the existing literature on the subject retrieved from the PubMed and Google Scholar scientific databases for the period from 2014 to 2024. The research included meta-analyses, randomized controlled trials, and systematic reviews, with inclusion criteria based on publication date, topic relevance, and keywords. For the identification of relevant articles, the search terms were used: "neuroinflammation", "neurodegeneration", "Alzheimer's disease", "microglia", "gut microbiome" and "oxidative stress".

3. RESULTS AND DISCUSSION

Numerous articles were collected from the data set using keywords, which were then subjected to a title and abstract screening process. Ultimately, 54 articles were included in the comprehensive analysis of results and discussion. The data analyzed pertained to the relationship between neuroinflammation, neurodegeneration, and Alzheimer's disease, comprising 38 articles. A total of 16 articles presented various treatment options. The following subsections present a summary of the information collected.

The relationship between neuroinflammation and neurodegeneration

The term "neuroinflammation" is used to describe a chronic inflammatory process. The causes of neuroinflammation are numerous and include infections, brain injury, autoimmunity, and the toxic effects of metabolites. Additionally, environmental pollutants and the process of aging can also contribute to the development of neuroinflammation. The etiology of neuronal inflammation is multifactorial. These processes include dysfunction of the blood-brain barrier, dysregulation of the microbiota, dysregulation of microglia, and oxidative stress. The following section will discuss these mechanisms in further detail. In the future, they may prove to be a valuable source of insight into the development of new therapeutic targets for the treatment of neurodegenerative diseases.

The intestinal microflora

The intestinal microflora is analogous to the ‘gut brain’ and encompasses bacteria, archaeons, fungi, viruses, and protozoa. These biochemical compounds exert an influence on CNS (central nervous system) function. The microflora plays a pivotal role in regulating a number of vital physiological processes, including the hypothalamic-pituitary-adrenal axis, immune function, the blood-brain barrier, neurogenesis, and myelogenesis. The composition of the microflora can be modified by many factors, including the delivery mode, stress, physical activity and type of diet, gastrointestinal infections, use of antibiotics, probiotics, and others (Cresci and Bawden, 2015). An imbalance in the microflora can result in the development of neurological disorders, including neurodegenerative diseases.

An increase in intestinal permeability may result in the onset of inflammation within the central nervous system, a process that is mediated by the action of inflammatory cytokines (Giau et al., 2018). A growing body of evidence indicates that patients with

Alzheimer's disease exhibit enhanced gastrointestinal permeability to Gram-negative bacteria, which possess lipopolysaccharide (LPS) within their cell membranes. In comparison to an age-matched control group, the mean level of LPS in the cortex of AD patients was found to be 26 times higher than that typically observed in a healthy population, with the plasma LPS concentration being three times higher than that observed in a control group of healthy subjects (Zhao et al., 2017).

Wykazano, że dysregulacja w obrębie mikrobiomu jelitowego może nasilać akumulację β-amyloidu. Badania pokazują, że u starszych pacjentów z zaburzeniami funkcji poznawczych liczebność w przewodzie pokarmowym dwóch bakterii przeciwzapalnych Bacteroides fragilis i Eubacterium rectale, jest mniejsza w porównaniu z bakteriami prozapalnymi (np. Escherichia coli i Shigella) (Garcez et al., 2019). The presence of the above-mentioned pathogenic bacteria in the gastrointestinal tract is associated with increased production of pro-inflammatory cytokines and activation of the NLRP3 (NOD-like receptor family, pyrin domain containing 3) inflammasome, and this promotes β-amyloid accumulation and inflammation, which play a pathogenetic role in Alzheimer's disease (Cattaneo et al., 2017).

Also, subsequent studies have confirmed the association of E. coli and Shigella with neuroinflammation. The researchers examined the microflora of 40 β-amyloid-positive patients with cognitive impairment, 33 β-amyloid-negative patients with cognitive impairment, and control participants. The number of E. coli and Shigella bacteria in the group with amyloid and cognitive impairment was higher in comparison to the other groups. Acinetobacter rectum and Bacteroides fragilis bacteria were reduced (Zou et al., 2023). A meta-analysis of 11 studies comprising 427 patients with Alzheimer's disease (AD) revealed a markedly diminished gut microbiota biodiversity in these patients compared to controls. Conversely, no decline in diversity was observed in patients with mild cognitive impairment (MCI) (Hung et al., 2022).

Furthermore, additional studies have corroborated the correlation between diminished gut microflora biodiversity and AD. A total of ten bacterial types exhibited a significant correlation with AD, four of which demonstrated a notable association with the APOE (apolipoprotein E gene) risk allele (Cammann et al., 2023). One study examined the correlation between APOE genotype and the gut microbiome composition in humans and transgenic mice. The APOE genotype was demonstrated to be linked to particular gut microbiome profiles in humans and mice. Of particular relevance in this context were the Prevotellaceae and Ruminococcaceae, as well as several genera of butyrate-producing bacteria (Tran et al., 2019). In light of the evidence demonstrating the impact of gut microflora on brain function, it is valuable to examine the compounds that mediate this process.

It is of particular significance that the microflora secretes toxins and short-chain fatty acids, which modulate intestinal permeability and numerous immune functions (Cammann et al., 2023). The effect of SCFAs (short-chain fatty acids) on CNS function is dependent on the specific type of fatty acid involved, with the potential to exert either a beneficial or detrimental influence. These processes occur via three principal pathways: Immune modulation, and the endocrine pathway (by modulating the action of hormones produced in the gut and by regulating the levels of specific neurotransmitters and neurotrophic factors). The microflora can influence brain function by producing precursors of neurotransmitters.

One such neurotransmitter is gamma-aminobutyric acid (GABA), which indirectly stimulates the secretion of 5-HT (serotonin 5-HT receptor) by cells in the gut wall and influences the expression of brain-derived neurotrophic factor (BDNF) and DA (dopamine agonists) in the brain (Palm et al., 2015). An intriguing compound is trimethylamine N-oxide (TMAO), a molecule that is produced as a byproduct of intestinal bacterial metabolism. TMAO is a pro-apoptotic compound that has been demonstrated to induce neurodegeneration, increase oxidative stress, damage mitochondria, and inhibit rapamycin target protein signaling. TMAO has been demonstrated to induce neuroinflammation and facilitate the accumulation of β-amyloid and tau proteins through the dysregulation of the gut microbiota (Li et al., 2018).

The blood-brain barrier

The blood-brain barrier (BBB) represents a physical and biochemical barrier between the blood vessels and the nervous tissue. The structure of the blood-brain barrier consists of brain endothelial cells capillaries, astrocytes, and pericytes. The connections between the endothelial cells are called tight junctions and adhesive junctions. Tight junctions are integral to the functionality of the BBB, comprising a complex network of proteins, including occludins, claudins, and cell adhesion proteins. As a consequence of the natural aging process, morphological alterations occur in the brain capillaries, which in turn result in a reduction in the integrity of the BBB. It is of the greatest importance for the CNS to function correctly so that the blood-brain barrier is maintained in a healthy state.

Damage to the intestinal barrier and the BBB represents a significant contributing factor to the development of neuronal inflammation and numerous neurological diseases (Mou et al., 2022). One short-chain fatty acid produced by the intestinal microflora, propionate, has been demonstrated to exert a protective effect on BBB integrity and the protection of tight junction proteins. Similarly, butyrate has been shown to have a neuroprotective effect in an experimental mouse model of Parkinson's disease, increasing the expression of occludin and ZO-1 (zonula occludens-1) protein (Knox et al., 2022). A principal function in maintaining barrier integrity is attributed to pro-inflammatory IL-6 (interleukin-6), which exerts its effects on brain microvascular endothelial cells (Blecharz-Lang et al., 2018).

TNF-α (tissue necrosis factor-α) also plays a significant role in the functioning of the BBB. It has been demonstrated that human brain microvascular endothelial cells, when exposed to TNF-α at a dose of 0-100 ng/ml, induce IL-6 expression and IL-6 family receptor release and expression (Rochfort et al., 2016). Furthermore, additional studies have corroborated that the administration of TNF-α or IL-6 results in a dose- and time-dependent reduction in the expression of interendothelial junction proteins, which affects endothelial cell permeability (Rochfort et al., 2014). Furthermore, blood-brain barrier dysfunction impedes the transport of β-amyloid from the brain into the peripheral circulation. This is associated with decreased levels of LRP-1 (lipoprotein receptor 1) and increased levels of RAGE (receptor for advanced glycation endproducts), which contribute to β-amyloid accumulation (Cai et al., 2018).

Neuroimaging was also employed in this study, which demonstrated the presence of dysfunctional blood-brain barrier (BBB) characteristics in the hippocampus of subjects diagnosed with MCI when compared to the control group. Contrast-enhanced magnetic resonance imaging (DCE) was utilized in the investigation. The leakage of the gadolinium contrast agent into the brain was observed, and the regional BBB permeability was determined. The extent of BBB damage was found to correlate with elevated levels of soluble platelet-derived growth factor in cerebrospinal fluid β (PDGFRβ), which serves as a marker of pericyte damage (Sweeney et al., 2018).

Microglia

A principal element of the CNS immune system is the microglia. Microglia cells are classified as central nervous system-specific macrophages, representing 5-12% of all CNS cells. Active microglia can be classified into two distinct phenotypes: The M1 phenotype, which is anti-inflammatory, and the M2 phenotype, which is pro-inflammatory. Microglia activation is initiated in response to damage to the CNS. Upon activation, microglia cells begin to produce a multitude of cytokines, chemokines, and cytotoxic compounds, including TNFα, IL-6, IL-1β (interleukin 1β), and NO (nitric oxide). This process initiates the immune response. The resulting inflammation is a consequence of the repair processes and neuronal damage (Erny et al., 2017). The activation of microglia is mediated by a number of different mechanisms.

Microglia cells express a multitude of receptors on their surface, including those that facilitate the recognition of pathogen-associated molecules, complement receptors, and receptors for cytokines and chemokines. Microglia develop towards a pro-inflammatory M1 phenotype upon detection of damage- or pathogen-associated molecular patterns (DAMPs and PAMPs) by pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs). It has been demonstrated that there is a considerable expression of PRRs in the context of Alzheimer's disease (AD). Prolonged activation of the TLR2 and TLR4 receptors is of particular significance in the pathogenesis of AD, as it has been demonstrated to induce β-amyloid production (Rajesh and Kanneganti, 2022).

Inhibition of TLR2 has been demonstrated to diminish glial cell reactivity, reduce β-amyloid levels, and enhance cognitive function (McDonald et al., 2016). The purinergic receptor P2X7 plays an equally pivotal role in microglia function, as evidenced by findings from mouse studies. Activation of the P2X7 receptor on microglia results in the release of pro-inflammatory cytokines. Activation of microglia increases its migratory capacity to β-amyloid plaques, yet simultaneously impairs its phagocytic capacity, which ultimately results in β-amyloid accumulation (Huang et al., 2024). In February 2024, researchers from Australia published the results of their work, in which they developed novel monocultures of microglia cells (MDMi) and co-cultures of neuroglia cells (ReNcell VM) using three-dimensional technology.

The researchers generated and characterized MDMi from sixteen AD patients and matched controls, as well as profiled cytokine responses to treatment with anti-inflammatory drugs such as dasatinib and spiperone. The 3D culture of MDMi demonstrated alterations in cell-cell interactions, growth factor and cytokine secretion profiles, and β-amyloid responses. The objective of this study was to facilitate the advancement of personalized pharmacological strategies for the treatment of Alzheimer's disease. This represents a

highly novel approach to the development of effective AD treatment strategies based on the modification of the inflammatory response of microglia cells (Cuní-López et al., 2024).

Oxidative stress

Oxidative stress is another important factor in the development of neurodegenerative diseases. The role of this factor in the pathogenesis of a multitude of diseases is not limited to neurological disorders. Its involvement has also been observed in the development of neoplastic, cardiovascular, renal, and pulmonary pathologies, in addition to its impact on the aging process (Jomova et al., 2023). Oxidative stress may be defined as an imbalance between the levels of reactive oxygen species (ROS), and the body's ability to detoxify them using antioxidants. Unreduced ROS can damage proteins, DNA, and lipids. Excess ROS has pro-inflammatory effects and induces cell apoptosis. Given the high metabolic rate associated with the brain, it is particularly susceptible to reactive oxygen species.

Additionally, the brain contains large amounts of redox-active metals - iron and copper - which participate in ROS formation reactions. Moreover, the high levels of polyunsaturated fatty acids in neuronal cell membranes serve as substrates in the lipid peroxidation process (Kim et al., 2015). It is certain that oxidative stress and neuroinflammation are interconnected, thus indirectly linking oxidative stress with neurodegeneration and brain structural changes (Teleanu et al., 2022). ROS is a significant modulator of microglial inflammatory responses. In the brain, ROS are primarily produced by NADPH oxidase (NOX2). Reactive oxygen species affect microglia by regulating important signaling pathways such as NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells).

NFκB controls the expression of pro-inflammatory genes in microglia. Studies have shown that the administration of H2O2 (hydrogen peroxide) or the induction of H2O2 release by IL1β or LPS can activate this signaling pathway in various cell types, thereby inducing inflammation (Simpson and Oliver, 2020). It has been demonstrated that in the course of neurodegenerative diseases, oxidative stress can exacerbate the processes of production and accumulation of β-amyloid and tau protein. Studies on mouse models of AD have shown elevated levels of hydrogen peroxide and protein and lipid peroxidation, which are pathogenic factors in neuroinflammation (Kim et al., 2015).

Similarly, the deposition of α-synuclein, a protein associated with Parkinson's disease, is linked to oxidative stress. An extremely important compound responsible for neutralizing ROS in the brain is glutathione. Excess ROS and glutathione deficiency can play a significant role in neurodegenerative processes. Research has shown that reduced glutathione levels are characteristic of MCI, but no decline in its levels has been observed in AD, suggesting that the deficiency of this antioxidant is characteristic of the early stages of AD (Song et al., 2021).

Alzheimer's Disease

Alzheimer's Disease represents the most common cause of both dementia and age-related cognitive decline, occurring in 90% of cases in individuals over 65. Early onset cases are associated with mutations in amyloid and presenilin genes. The initial symptoms are often unnoticed and can be mistaken for aging or stress. The amyloid cascade hypothesis is the most widely accepted theory to explain the etiology of AD. The cholinergic hypothesis focuses on the reduced synthesis of the neurotransmitter acetylcholine. Based on this hypothesis, the primary drugs for AD, donepezil and rivastigmine, were developed, but these drugs have limited efficacy. Another hypothesis links AD with a generalized inflammatory state in the brain. Given the restricted efficacy of the prevailing pharmacological agents, targeting chronic inflammation might become a key approach in the prevention and treatment of AD.

In one study, 43 MCI patients underwent neuroimaging using PET 11C-PK11195 to measure inflammatory changes and PET 11C-PiB to determine the β-amyloid load. Furthermore, 22 subjects underwent positron emission tomography (PET) with 18F-flortaucipir to assess tau protein burden. The study lasted two years and aimed to confirm the relationship between inflammation and β-amyloid and tau levels in MCI patients. Four patient groups were described: MCI patients with high initial 11C-PiB uptake, indicating elevated inflammation that decreased in cortical areas over two years while their β-amyloid levels increased; MCI patients with low/normal initial 11C-PiB uptake, but whose levels increased over two years, classified as prodromal AD with low initial amyloid deposition; MCI patients with low initial 11C-PiB uptake that remained stable, classified as unrelated to AD; and MCI cases with high initial 11C-PiB and 18F-Flortaucipir uptake, showing increased tau burden and correlated inflammation over two years.

The study demonstrated that increasing β-amyloid levels are correlated with microglial activation, and rising tau protein levels are associated with increased inflammation (Ismail et al., 2020). A meta-analysis compiled clinical-control studies investigating the level of translocator protein (TSPO) using positron emission tomography (PET) between a healthy control group and individuals with MCI or AD. TSPO is a protein located in the outer mitochondrial membrane, involved in various cell functions, including cellular respiration, steroidogenesis, immune responses, apoptosis, and cell proliferation. Healthy brain tissue contains small amounts of TSPO, mainly present in microglia and astrocytes. Its expression increases in pathological conditions of various etiologies, including traumatic CNS injury, neurodegenerative diseases, and epilepsy (El-Chemali et al., 2022).

The meta-analysis included 28 studies with 755 participants and 37 brain regions. Compared to the control group, AD participants had elevated TSPO levels throughout the brain, particularly in the frontotemporal areas. MCI individuals had moderately elevated TSPO levels, mainly in the neocortex. The study confirmed the association between increased neuroinflammation and MCI and AD (Bradburn et al., 2019). PET imaging appears to have significant clinical relevance and could play an important role in monitoring AD. Another meta-analysis gathered 40 and 39 studies on MCI and AD, respectively, to identify metabolic changes in the brain related to neuroinflammation, oxidative stress, and mitochondrial dysfunction in these patients.

The study found metabolic changes in the form of reduced N-acetyl aspartate and creatine levels and increased myoinositol levels in MCI and AD, but reduced glutathione levels only in MCI, and impaired energy metabolism in AD. These changes were most pronounced in the hippocampus, which is responsible for memory processes (Song et al., 2021). Activation of the NLRP3 inflammasome is a significant contributor to the inflammatory pathogenesis of AD. Activation of the NLRP3 inflammasome results in the activation of caspase-1 and the subsequent release of pro-inflammatory cytokines, including IL-1β and IL-18 (interleukin-18). β-amyloid acts as an activator of this inflammasome (Kelley et al., 2019). Tau protein is also responsible for NLRP3 inflammasome activation; loss of its function reduces tau deposition (Ising et al., 2019).

Given the inflammatory basis of Alzheimer's disease, are there biomarkers of neuroinflammation? For AD, the most commonly assessed inflammatory parameters are IL-1β, IL-6, TNF-α, and CRP (C-reactive protein). A meta-analysis evaluated whether levels of pro-inflammatory markers, including interleukin-1β, TNF-α, and C-reactive protein, are higher in older adults with Alzheimer's disease, including patients with depression. The study included 1,645 Alzheimer's patients and 14,363 control group members. The results showed significantly elevated IL-1β levels in Alzheimer's disease compared to the control group, with no differences in IL-6, TNF-α, and CRP levels between older adults with Alzheimer's and the control group (Ng et al., 2018).

Another meta-analysis of 13 studies found increased CRP and IL-6 levels, as well as α1-antichymotrypsin, lipoprotein-associated phospholipase A2 activity, and fibrinogen in patients with dementia of various etiologies, but none were significantly associated with Alzheimer's disease (Darweesh et al., 2018). In 2019, a systematic review and meta-analysis included 170 studies involving 9,842 AD patients, 3,526 MCI patients, and 9,002 control group members. It evaluated inflammatory biomarker results from blood or cerebrospinal fluid in MCI and AD patients. The findings were clear - significantly altered inflammatory biomarker levels were confirmed in AD and MCI patients compared to the control group.

Several biomarkers, such as high-sensitivity CRP (hs-CRP), IL-6, soluble tumor necrosis factor receptors 1 and 2 (sTNFR1 and 2), α1-antichymotrypsin (α1-ACT), IL-1β, soluble CD40 ligand-receptor, and IL-10 in cerebrospinal fluid, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor β1, soluble TREM2 (sTREM2), YKL-40, nerve growth factor, and visinin-like protein-1 (VILIP-1), had elevated levels in AD compared to the control group. In MCI, increased levels of sTNFR2, IL-6, and MCP-1 were observed, along with lower IL-8 levels in the blood, and elevated YKL-40, VILIP-1, and sTREM2 levels in cerebrospinal fluid (Shen et al., 2019). Thus, numerous laboratory and imaging studies confirm the link between the inflammatory process and Alzheimer's disease. However, these relationships require further research to develop the best therapeutic strategies for AD patients.

Alternative Therapeutic Methods and Future Potential Treatments

Advancements in scientific research, particularly in the field of neurology, offer promising prospects for the future development of effective and safe medications for the treatment of AD. Currently, in Poland, the standard drugs used for Alzheimer’s disease are acetylcholinesterase inhibitors – donepezil and rivastigmine, and in the later stages, an N-methyl D-aspartate (NMDA) receptor antagonist – memantine. These drugs were registered about 20 years ago (Table 1). Illustrates the potential alternative therapeutic avenues that may be employed in the management of neurodegenerative disorders.

Table 1 Alternative therapeutic methods and future potential treatments for neurodegenerative disorders.

Substance name	Studies	Summary
Aducanumab	Aducanumab, a monoclonal antibody, has been approved by the FDA. In 2022, two randomized, double-blind, placebo-controlled phase III trials of aducanumab were conducted in patients with early Alzheimer's disease. Initially, 3285 patients participated, but 1812 completed the study. Patients received either a low dose of aducanumab, a high dose, or a placebo intravenously for 76 weeks. The outcome measure was a scale assessing both function and cognitive abilities. Both trials were terminated early due to a futility analysis, which questioned the reliability of the results. However, in both studies, a dose- and time-dependent reduction in Alzheimer's disease pathophysiological markers (tau protein in PET, p-tau in cerebrospinal fluid, and p-tau181 in plasma) was observed. The most frequently observed adverse event associated with aducanumab was an abnormality identified through magnetic resonance imaging (MRI), with patients experiencing serious and severe symptoms, including seizures, which in rare cases required hospitalization (Budd-Haeberlein et al., 2022).	Further high-quality clinical trials are undoubtedly necessary to determine the efficacy and safety of aducanumab.
Dimethyl fumarate (DMF)	In efforts to develop effective AD therapies, researchers are investigating the use of DMF, a clinically used drug to activate the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway. Studies have shown that Nrf2 alleviates neuroinflammation in mouse models of neurodegenerative diseases. DMF has antioxidant, anti-inflammatory, and anti-apoptotic effects, prompting its potential use in medicine. Currently, this compound is used in the treatment of psoriasis and multiple sclerosis (Majkutewicz, 2022). In mouse studies, DMF reduced amyloid-β-induced memory impairment and hippocampal atrophy in AD mice, but not in AD mice with Nrf2 knockout. DMF delays the progression of AD through the activation of the Nrf2 pathway (Sun et al., 2022).	Research indicates that DMF is a potential therapeutic option for AD patients.
Flavonoids	Flavonoids are classified as polyphenols, naturally occurring substances in many plants, possessing antioxidant and anti-inflammatory properties. Studies have shown that these compounds exhibit neuroprotective effects. Flavonoids regulate signaling pathways such as the nuclear factor kappa pathway, the Toll-like receptor pathway, and the erythroid 2-related factor 2 pathway. In Alzheimer's disease (AD), they prevent β-amyloid aggregation and neurofibrillary tangle formation (Minocha et al., 2022). There are numerous review articles on flavonoids and Alzheimer's disease, but fewer randomized controlled clinical trials. A systematic review encompassing 37 studies revealed that elevated flavonoid consumption is linked to enhanced cognitive performance and a diminished risk of cognitive decline, although certain exceptions did emerge. A quantitative meta-analysis	It is highly recommended that patients consume a diet rich in flavonoids due to their high safety profile and numerous potential benefits.

	revealed an inverse relationship between all flavonoids and cognitive impairment (Godos et al., 2024).	
Coenzyme Q10 and Vitamin E	A systematic review and meta-analysis of studies measuring CoQ10 levels in tissues of patients with dementia and a control group showed that, compared to the control group, patients with AD had similar plasma CoQ10 levels. However, mouse models of AD demonstrated the potential role of CoQ10 treatment in AD and memory improvement in older rodents (Jiménez-Jiménez et al., 2023). Research on neurodegenerative diseases observed high levels of formaldehyde and low levels of CoQ10 in these patients. Excess formaldehyde inactivated CoQ10. Subsequently, water-soluble nano micellar CoQ10 showed positive therapeutic effects, suggesting that this compound may benefit patients with neurodegenerative diseases (Xu et al., 2022). Experiments with neurodegenerative disease models proved that vitamin E supplementation improves memory, cognitive functions, and motor functions. Vitamin E supplementation reduces β-amyloid deposition in the brain, decreases tau protein hyperphosphorylation, and increases superoxide dismutase levels and brain-derived neurotrophic factor (BDNF) in rodents (Da-Cunha-Germano et al., 2023). In 2022, a 12-month randomized, double-blind, placebo-controlled clinical trial was conducted among patients with mild and moderate Alzheimer's disease. They consumed daily: 22 mg of carotenoids, 1 g of fish oil (500 mg DHA, 150 mg EPA), and 15 mg of vitamin E or a placebo. The studies unequivocally showed a statistically significant difference in AD symptom severity measurements (memory and mood), with these parameters improving in patients who consumed the above supplementation for 12 months compared to the control group (Nolan et al., 2022).	There are recommendations for patients to consume a diet high in vitamin E due to its high safety profile and numerous potential benefits. Coenzyme Q10 is also recommended.
Probiotics	Research on the use of probiotics in neurological diseases is promising. One systematic review considering 22 articles provided evidence supporting the use of probiotics in patients with AD with positive effects. The mechanism of probiotics in AD is not fully understood, but short-chain fatty acids produced by gut bacteria of the genera Bacteroides, Clostridium, Lactobacillus, Bifidobacterium, and Eubacterium are believed to play a significant role (Naomi et al., 2021). Another meta-analysis considering five studies involving a total of 297 people with AD or MCI showed a significant increase in improvement in cognitive functions in patients with AD or MCI. Additionally, there was a significant reduction in malondialdehyde and high-sensitivity C-reactive protein levels in comparison to the control group, which was assessed as the probable mechanism of probiotics (Den et al., 2020). A further article, comprising a total of 35 studies, 26 of which were conducted on animal models and nine on humans,	However, there are few high-quality human studies evaluating the impact of probiotics on AD, necessitating large-scale studies to officially confirm their effectiveness.

	demonstrated that probiotics confer neuroprotective benefits can mitigate cognitive decline, and regulate gut microbiota dysbiosis. The most commonly used in the included trials were Bifidobacterium and Lactobacillus species, considering both single-strain and multi-strain probiotics (Ji and Shen, 2021).	
Non-steroidal anti-inflammatory drugs (NSAIDs)	There is a large number of studies on the use of NSAIDs in Alzheimer's disease. These drugs are commonly used and available over the counter. One study showed that the use of the classic NSAID, acetylsalicylic acid, was associated with a reduced risk of Alzheimer's disease. Researchers conducted a Mendelian randomization analysis for two samples to check if the use of aspirin, in this case, genetically substituted, was causally linked to the risk of AD. The study was conducted in the UK Biobank, covering the entire genome (GWAS, genome-wide association study) (Ding et al., 2023). Nevertheless, a meta-analysis encompassing 14 studies (eight cohort studies and six case-control studies) revealed that NSAIDs do not exert a protective effect on AD (Asthana et al., 2023). Also, a case-control study on 19,114 participants lasting 4.7 years, with further evaluation for dementia in 964 participants, showed no efficacy of aspirin in reducing the risk of AD, MCI, or cognitive decline. The study used acetylsalicylic acid at a dose of 100 mg daily or a placebo (Ryan et al., 2020).	Studies on classical anti-inflammatory drugs leave some uncertainties.
Genetic engineering	In the search for effective AD treatments, genetic engineering achievements are also being utilized. Thanks to innovative technologies, scientists aim to reprogram microglial cells to treat neurological diseases. It is currently possible to promote microglial polarization towards a pro-inflammatory phenotype or to suppress its hyperactivation, in order to transform it into an anti-inflammatory phenotype. In AD, microglial hyperactivation is suppressed, while the pro-inflammatory microglial phenotype is attempted to be used in diseases such as glioblastoma. The main methods of reprogramming microglia are genetic targeting and therapeutic modulation (Luo and Sugimura, 2024).	Genetic engineering represents the future of medicine and may be used in the future to treat neurodegenerative diseases.
Inflammasomes	Inflammasomes, particularly the NLRP3 inflammasome, could become a therapeutic target in AD treatment. However, no drugs modifying inflammasome function have been developed yet, but with significant medical advancements, this is likely a matter of time (White et al., 2017).	

4. CONCLUSION

It is now clear that neuroinflammation plays an important role in the pathogenesis of the neurodegenerative disease. This is supported by both imaging studies and studies assessing levels of inflammatory biomarkers. The pathogenesis of neuronal inflammation is multifactorial and likely not yet fully understood. Contributing factors include blood-brain barrier dysfunction, microbiome dysregulation, microglial dysfunction, and oxidative stress. Further research on the significance of neuroinflammation in Alzheimer's disease and other, rarer neurodegenerative diseases is essential.

Moreover, therapeutic interventions aimed at combating inflammatory processes in the brain have shown positive effects. A better understanding of the mechanisms underlying the pathogenesis of neurodegenerative diseases will facilitate the development of improved clinical care strategies for patients. It is advisable to include regulation of the body's inflammatory response as part of the treatment regimen for Alzheimer's disease.

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Author's Contributions
Agata Pisklak: Conceptualization; software; resources; investigation; data curation; writing - rough preparation; supervision; project administration.
Kinga Filipek: Methodology; resources; writing - rough preparation; visualization.
Hanna Behrendt: Investigation; writing - rough preparation; writing - review and editing.
Marcin Głód: Formal analysis; resources; writing - review and editing.
Marta Węgrzynek: Formal analysis; data curation; writing - rough preparation.

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Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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