Essays

Increased Incidence of Alzheimer's Disease: Lifestyle and Supplementation with Nutraceuticals and Probiotics as New Prevention and Treatment Strategies

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ABSTRACT: Alzheimer's disease is a neurodegenerative disorder that mainly affects individuals over the age of 60, progressively rendering them unable to care for themselves. The incidence of the disease has increased dramatically in recent decades, posing a significant challenge to healthcare systems worldwide. Currently, there is no definitive and effective treatment, partly because the etiopathogenesis of the disease has not been fully elucidated. The disease, characterized histologically by amyloid plaques and neurofibrillary tangles, has very likely a multifactorial etiology. Neuroinflammation is thought to be the primary cause of the neurotoxicity observed in brain areas, including hippocampus and prefrontal cortex. Innovative methodologies and new tools derived from artificial intelligence have allowed us to define several risk factors and identify nutraceuticals and probiotics capable of counteracting neuroinflammation and disease progression.

KEYWORDS: Alzheimer's disease; neuroinflammation; oxidative stress; microglia; nutraceuticals; probiotics

1. Introduction

The rising incidence and mortality associated with neurodegenerative diseases, particularly Alzheimer's disease (AD), is a growing public health concern. The growing prevalence of the disease poses significant financial challenges, as patients with severe AD require intensive long-term care.[1] In 2015, the global economic burden of dementia was estimated at $818 billion.[2] These are highly debilitating diseases that undermine patients' ability to live independently and pose increasingly

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[1] S. NIZAMI, H. HALL-ROBERTS, S. WARRIER *et al.*, *Microglial inflammation and phagocytosis in Alzheimer's disease: Potential therapeutic targets*., in *Br J Pharmacol,* 176, 2019, 3515–32.

difficult and emotional challenges for family members and caregivers in managing the patient. Unfortunately, despite the enormous advances in contemporary medicine and the accumulation of relevant knowledge over the past decades, there remains a continuing shortage of effective drugs and therapies. The need to intensify prevention efforts, improve the quality of care, and adopt targeted policies that address the complexities of disease management is therefore highlighted.

2. Pathophysiological Process

Changes Alzheimer's disease is the most common form of dementia, characterized by the extracellular senile plaques, formed by the accumulation of amyloid peptide and the presence of intracellular tangles of hyperphosphorylated tau protein. This histopathological picture is initially accompanied by synaptic rarefactions and then neuronal death in certain brain regions, such as the hippocampus and prefrontal cortex. At the macroscopic level, there is a progressive reduction of the cerebral cortex, corresponding to an enlargement of the cerebral ventricles. The morphological characterization of AD is characterized by cerebral atrophy and enlargement of the cerebral ventricles.[3] The morphological that characterize the development of this chronic neurodegenerative disease result in specific cognitive impairments. These initially affect memory processes with short-term memory loss, and then affect normal daily activities, resulting in a loss of independence, language difficulties, and spatial and temporal disorientation. The first and most common symptom of AD is short-term memory loss. As the disease progresses, symptoms such as aggression, irritability, agitation, confusion or difficulty recognizing objects (agnosia), language problems (aphasia), impaired motor skills (apraxia), inattention, behavioral disturbances, executive dysfunction, and long-term memory loss frequently occur. This is due to alterations in specific brain regions such as the hippocampus, entorhinal cortex, and amygdala, which are responsible for learning, memory, emotion, and behavior.[4]

To date, more than a century after neurologists Alzheimer and Perusini described the disease, its etiopathogenesis has not been identified. What is extremely clear, however, is the sharp increase in incidence, also in relation to increased life expectancy, given that the sporadic, non-familial form of Alzheimer's disease mostly manifests after age 50. Current estimates indicate that the number of people

[2] A. Wimo, M. Guerchet, G.C. Ali *et al.*, *The worldwide costs of dementia 2015 and comparisons with 2010, in Alzheimers Dement,* 13, 2017, 1–7.

[3] B.P. Imbimbo, J. Lombard, N. Pomara, *Pathophysiology of Alzheimer's disease, in Neuroimaging Clin N Am*, 15(4), 2005, 727-53.

[4] E. Onofri, S. Ricci, M. Mercuri *et al.*, *Cognitive fluctuations in connection to dysgraphia a comparison of Alzheimer's disease with dementia Lewy bodies,* in *Clinical Interventions in Aging*, 10, 2015, 623-33. M. Nasb, W. Tao, N. Chen, *Alzheimer's Disease Puzzle: Delving into Pathogenesis Hypotheses,* in *Aging Dis*, 15, 2024, 43–73. B. Highet, J.A. Wiseman, H. Mein *et al., PSA-NCAM Regulatory Gene Expression Changes in the Alzheimer's Disease Entorhinal Cortex Revealed with Multiplexed in situ Hybridization,* in *J Alzheimers Dis,* 92(1), 2023, 371-390. K. Kumar, A. Kumar, R.M. Keegan *et al.*, *Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease, in Biomed Pharmacother,* 98, 2018, 297-307.

affected by Alzheimer's disease worldwide currently reaches 50 million, and if the upward trend continues, the number is expected to reach 82 million in 2030 and 152 million in 2050.[5]

3. Familial AD (Early Onset Alzheimer's Disease, EOAD) and Sporadic AD (Late Onset Alzheimer's Disease, LOAD)

Over the age of 65, one in ten people is affected by AD, and approximately 35% of people aged 85 and older have Alzheimer's disease. Depending on the age of onset, two types of AD are distinguished: familial AD or EOAD and sporadic AD or LOAD.[6] People between the ages of 30 and 60 are usually affected by EOAD. Sixty percent of early-onset forms are called familial as multiple members of the same family are affected, and approximately 13% of these cases are due to a mutation affecting the presenilin-1 (PSEN1), presenilin-2 (PSEN2), and beta-amyloid precursor protein (APP) genes. This is transmitted in an autosomal dominant fashion, meaning that 50% of offspring may be carriers of the mutation. LOAD, or sporadic form, affects individuals over the age of 60.[7] There are genetic variants associated with an increased risk of Alzheimer's disease. The best known is a variant of the gene encoding apolipoprotein E (APOE), the APOE4 variant.[8] In fact, carriers of the ApoE4 variant of the gene encoding apolipoprotein E have an 8- to 18-fold higher risk of developing the sporadic form of AD compared to carriers of other haplotypes. It is well known that genetic association studies using SNPs have proven highly complicated due to the difficulty of examining the large number of subjects required to obtain reliable results. By applying artificial intelligence through machine learning (ML), it was possible to examine the genomic data of 41,686 individuals from the largest European AD consortium to investigate the effectiveness of various ML algorithms in replicating known results, discovering new loci, and identifying individuals at risk.[9] The ML study identified all previously identified genomically significant genetic variants and 22% of the associations resulting from larger meta-analyses. It also highlighted 6 new loci including variants mapping to ARHGAP25, LY6H, COG7,SOD1 and ZNF597, implicating alterations: in phagocytosis (ARHGAP25), in binding to the nicotinic acetylcholine receptor,[10] at the level of Oligomeric Golgi Complex Component 7 (COG7) whose mutations are associated with Congenital Disorders of Glycosylation (CDG)32,[11] at the level of SOD1 which plays an essential role in anti-oxidant defenses.[12]

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[5] https://www.alzint.org/resource/world-alzheimer-report-2021/ C.S. AGUZZOLI, K.J. ANSTEY, A. ATRI, *et al.*, *World Alzheimer Report 2024 Global Changes in Attitudes to Dementia*, *Alzheimer's Disease International*, London, UK, 2024.

[6] C.A. VALDEZ-GAXIOLA, F. ROSALES-LEYCEGUI, A. GAXIOLA-RUBIO *et al.*, *Early- and Late-Onset Alzheimer's Disease: Two Sides of the Same Coin?,* in *Diseases*, 12(6), 2024, 110.

[7] R.C. BARBER. *The genetics of Alzheimer's disease,* Cairo, 2012.

[8] A. CHRISTENSEN, C.J. PIKE, *APOE genotype affects metabolic and Alzheimer-related outcomes induced by Western diet in female EFAD mice,* in *FASEB J*, 33, 2019, 4054–4066.

[9] M. BRACHER-SMITH, F. MELOGRANA, B. ULM *et al.*, *Machine learning in Alzheimer's disease genetics,* in *Nat Commun*, 16, 2025, 6726.

[10] M. WU, C.Z. LIU, E.A. BARRALL *et al.*, *Unbalanced Regulation of α7 nAChRs by Ly6h and NACHO Contributes to Neurotoxicity in Alzheimer's Disease,* in *J Neurosci,* 41, 2021, 8461-8474.

[11] H. HAUKEDAL, K.K. FREUDE, *Implications of Glycosylation in Alzheimer's Disease,* in *Front Neurosci,* 14, 2021, 625348.

[12] L. CAO, Y.T. DONG, J. XIANG *et al., Reduced expression of SIRT1 and SOD-1 and the correlation between these levels in various regions of the brains of patients with Alzheimer's disease,* in *J Clin Pathol*, 71, 2018, 1090-1099.

4. Etiopathogenesis

The etiopathogenesis of AD is still not fully understood. Numerous studies undertaken since Selkoe[13] formulated the hypothesis that the disease resulted from the accumulation of amyloid peptides in senile plaques, have made it clear that AD is a complex, multifactorial disease, determined by complex interactions between glia and neurons and favored by a genetic predisposition and exposure to specific exogenous and endogenous stimuli.

The Aβ peptide, which accumulates in senile plaques, is formed following the proteolytic processing of a precursor protein, known as APP (amyloid precursor protein), by gamma-secretase, a multiprotein complex that releases Aβ peptides of varying lengths, implicated in the pathogenesis of AD. APP, a 100-140 kD protein encoded by a gene on chromosome 21q21.3, is a transmembrane protein with about ten known isoforms. It is expressed in various cell types; at the neuronal level, the 695-amino acid isoform is expressed, which is cleaved by the enzymes β-secretase and γ-secretase to generate Aβ peptides and oligomers that aggregate to form neurotoxic fibrils and plaques in the brain.[14]

Aβ aggregation promotes synaptic dysfunction, tau phosphorylation, mitochondrial dysfunction, and the expression of autophagy-related genes and apoptotic proteins, contributing to neuronal death.[15]

Among the multiple factors involved in this disease, a significant role is played by the accumulation of amyloid-beta (Aβ), a 42-residue peptide whose production and clearance are finely regulated in the brain. Research has shown that impaired Aβ clearance is a significant factor in the progression of AD.[16]

5. Genetics and Epigenetics Factors Underlying AD Development

Much evidence points out that AD is a multifactorial disease, depending on the interplay between exposome, genetic and epigenetic factors. The Genome Wide association Study (GWAS) enabled the discovery of novel genetic associations with AD, beyond the well-established APOE ε4 allele, that, already known reduces the efficiency of microglial clearance of Aβ, further exacerbating amyloid accumulation. Five new loci have been identified, including IQCK, ACE, ADAM10, ADAMTS1, and WWOX, that are involved in lipid metabolism, amyloid precursor protein (APP) processing, tau biology, and neuroinflammation.[17]

It is known that, although present, not all genes are expressed at the same time and in all cells. Gene expression characterizes the physiological properties and any pathological processes that occur in cells and directs the fundamental characteristics of organs and systems. Therefore, there is a temporal and tissue modulation of the expression of various genes, the correct balance of which is the basis of homeostatic mechanisms. The science that studies the machinery underlying this modulation is called epige-

[13] D.J. Selkoe, *The molecular pathology of Alzheimer's disease,* in *Neuron*, 6, 1991, 487–498.

[14] M. Pasteris, S. Cakir, A. Bellizzi *et al*., *Alternative splicing in Alzheimer's disease: Mechanisms, therapeutic implications, and 3D modeling approaches,* in *J Alzheimers*, 2025.

[15] M.S. Hussain, N. Agrawal, B. Ilma *et al*., *Autophagy and Cellular Senescence in Alzheimer's Disease: Key Drivers of Neurodegeneration*, in *CNS Neurosci Ther*, 31(7), 2025.

[16] J. Zukowska, S.J. Moss, V. Subramanian *et al*., *Molecular Basis of Selective Amyloid-β Degrading Enzymes in Alzheimer's Disease*, in *FEBS J*, 291, 2024, 2999–3029.

[17] P. Tiwari, R. Dwivedi, M. Kaushik, M. Tripathi, R. Dada, *Genetics and Epigenetics of Alzheimer's Disease: Understanding Pathogenesis and Exploring Therapeutic Potential,* in *J Mol Neurosci*, 75, 2025, 72.

netics[18] and refers to changes in gene expression not coded in the DNA sequence, taking place without modifying the genotype. These changes are dependent on DNA methylation or hydroxymethylation, histone post-translational modifications, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs).[19] Epigenetic changes are plastic and include DNA methylation, which generally suppresses gene expression and at the level of brain is involved in memory formation and storage,[20] is obtained by adding a methyl group to cytosine. DNA methyltransferases (DNMTs) catalyze DNA methylation by shifting a methyl group from S-adenosyl methionine (SAM) to the fifth carbon of a cytosine residue, resulting in 5methyl Cytosine, mainly at the level ofCpG islands in the promoter region.[21] DNA methylation and demethylation may be dysregulated in the decreased cognition that is linked with neurodegeneration.[22]
Histone methylation is responsible for both transcriptional activation and repression and occurs mainly on arginine and lysine residues; generally, monomethylation is linked with transcription activation, whereas trimethylation has been connected to transcription repression. Histone acetylation has been linked to the formation of memory; it relaxes histone–DNA connections, resulting in a more open configuration that allows transcriptional machinery to reach gene promoters and upregulate transcription.

5.1. MicroRNAs

miRNA are small, non-coding RNA molecules that regulate gene expression at the posttranscriptional level by binding to the 3' untranslated regions (UTRs) of target mRNAs, leading to either their degradation or inhibition of translation. The dysregulation of several miRNAs has been connected to synaptic dysfunction, neuroinflammation and apoptosis. For example, miR-29a/b and miR-34a have been linked to AD, as they play roles in amyloid-beta (Aβ) accumulation and tau hyperphosphorylation. miR-29a/b specifically targets the BACE1 gene, which encodes the enzyme responsible for Aβ production. When these miRNAs are downregulated, BACE1 expression increases, leading to elevated Aβ levels and subsequent plaque formation.[23] In this connection a recent paper by Raia et al.[24] demonstrated that the expression of miR-29a and of its target, BACE1, are inversely correlated and that environmental conditions, such as modulation of one carbon metabolism by diet, modulate miR-29a through DNA methylation, that is MiR-29a is repressed in hypomethylating and expressed in hypermethylating conditions. In

[18] C.H. Waddington, *The epigenotype*, in *Int J Epidemiol*, 41, 2012, 10–13.
[19] Z. Firdaus, X. Li, *Epigenetic Explorations of Neurological Disorders, the Identification Methods, and Therapeutic Avenues*, in *Int J Mol Sci*, 25, 2024, 11658.
[20] C.H. Poon, Y.S. Chan, M.L. Fung, L.W. Lim, *Memory and neuromodulation: A perspective of DNA methylation*., in *Neurosci Biobehav Rev*, 111, 2020, 57–68.
[21] S. Maity, K. Farrell, S. Navabpour, S.N. Narayanan, T.J. Jarome, *Epigenetic mechanisms in memory and cognitive decline associated with aging and Alzheimer's disease*, in *Int J Mol Sci*, 22, 2021, 12280.
[22] J.M. Levenson, T.L. Roth, F.D. Lubin, C.A. Miller, I.C. Huang, P. Desai, L.M. Malone, J.D. Sweatt, *Evidence that DNA(cytosine-5) methyltransferase regulates synaptic plasticity in the hippocampus.* Much evidence points out that AD is a multifactorial disease, depending on the interplay between exposome, genetic and epigenetic factors. in *Biol Chem*, 281, 2006, 15763–15773.
[23] Z. Firdaus, X. Li, *op. cit*. See also M. Jain, S. Agarwal, A. Rana, A. Tiwari, N. Patil, *miRNA as an Ultimate and Emerging Diagnostic Approach for the Detection of Alzheimer's Disease*, in *MicroRNA* 12, 2023, 189–204 J. Zhao, D. Yue, Y. Zhou, L. Jia, H. Wang, M. Guo, H. Xu, C. Chen, J. Zhang, L. Xu, *The role of MicroRNAs in Aβ deposition and tau phosphorylation in Alzheimer's disease*, in *Front Neurol*, 8, 2017, 342.
[24] T. Raia, R.A. Cavallaro, L.D.F. Borges, S. Cinti, M. Bizzarri, I. Ferrer, M. Lucarelli, A. Fuso, *One-carbon metabolism modulates miR-29a-DNA methylation crosstalk in Alzheimer's disease,* in *Alzheimers Dement*, 21, 2025.

this way, ·miR-29 targets BACE1 mRNA reducing β-secretase expression and amyloidogenesis in Alzheimer's disease. As a consequence, miR-29a and other miRNAs hold potential as biomarkers for AD. Moreover, it may be possible to modulate these miRNAs to treat or even prevent the pathology.
Long Non-Coding RNAs (lncRNAs) are longer transcripts (>200 nucleotides) that regulate gene expression at multiple levels, including chromatin remodeling, transcriptional control, and posttranscriptional processing. A very important point that comes from epigenetics is that it will be possible to use new tools to set up new therapeutic treatments for Alzheimer's patients. The most promising treatments are HDAC inhibitors and DNA-demethylating agents. To control DNA methylation, two treatment approaches can be used: the first involves the use of DNMT inhibitors, and the second involves the administration of methyl donor substances such as folates and other B-group vitamins needed for SAM formation. Nutraceuticals such as polyphenols and isoflavones were showed to have the potential to modulate the epigenetic machinery.[25] Curcumin for example is an effective HDAC inhibitor and resveratrol acts as an activator of SIRT, a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase.

6. Glia and Neuroinflammation

Another potential factor contributing to the development of AD is neuroinflammation, which plays a critical role in both the initiation and progression of the disease. Long-term neuroinflammation can cause cellular damage by increasing inflammatory cells, producing reactive oxygen species (ROS), and causing significant changes in DNA.[26] The fact that many of the comorbidities associated with AD are linked to dysregulated metabolic pathways suggests that lifestyle variables play a role in the etiology of the disease. In this sense, lifestyle changes such as exercise and diet can interact with inherited susceptibility genes to improve cognitive abilities in AD patients.[27] The development of innovative treatments and the promotion of interventions aimed at promoting a healthy lifestyle are essential to improve the lives of people affected by this debilitating condition.[28]
Numerous studies have identified immunosenescence and neuroinflammation as the primary factors involved in the development of the disease.[29] The microenvironment that leads to the loss of specific neuronal populations, primarily in the hippocampus and prefrontal cortex, is thought to be dependent on the release of proinflammatory and neurotoxic factors, secondary to close interactions between neu-

[25] M. Mota, V. Porrini, E. Parrella *et al.*, *Neuroprotective epi-drugs quench the inflammatory response and microglial/macrophage activation in a mouse model of permanent brain ischemia,* in *Journal of Neuroinflammation, 17,* 2020, 361.
[26] S. Samanta, S. Chakraborty, D. Bagchi, *Pathogenesis of Neurodegenerative Diseases and the Protective Role of Natural Bioactive Components,* in *Journal of the American Nutrition Association*, 43, 2024, 20-32.
[27] T. Archer, S. Ricci, F. Massoni *et al.*, *Cognitive benefits of exercise intervention,* in *Clinica Terapeutica* 167, 2016, 180-85. P. Ricci, F. Massoni, L. Ricci *et al.*, *Quality of life in dementia sufferers: The role of diet and exercise. Current Alzheimer Research*, 15, 2018, 400-407. F. Galkin, O. Kovalchuk, D. Koldasbayeva *et al.*, *Stress, Diet, Exercise: Common Environmental Factors and Their Impact on Epigenetic Age,* in *Ageing Research Reviews*, 88, 2023, 101956. L. Yang, Z. Yuan, C. Peng, *Effects of Aerobic Exercise on Cognitive Function and Quality of Life in Patients with Alzheimer's Disease: A Systematic Review and Meta-Analysis,* in *BMJ Open,* 15, 2025.
[28] Y.L. Zhao, Y.N. Hao, Y.J. Ge *et al.*, *Variables Associated with Cognitive Function: An Exposome-Wide and Mendelian Randomization Analysis,* in *Alzheimer's Research and Therapy,* 17, 2025, 13.
[29] C. Franceschi, M. Capri, D. Monti *et al.*, *Inflammaging and Anti-Inflammaging: A Systemic Perspective on Aging and Longevity Emerged from Studies in Humans,* in *Mechanisms of Ageing and Development,* 128, 2007, 92–105.

rons and glia. While early research focused on beta-amyloid plaques and tau protein aggregates as the primary pathological factors, recent advances highlight the critical involvement of non-neuronal components, particularly astrocytes, microglia, oligodendrocytes, and NG2 glial cells, in disease progression. The recent development of new technologies, such as in situ glial imaging, in vitro cultures of human glial cells derived from induced pluripotent stem cells (iPSCs), and molecular analyses, has allowed to study the role of glia in specific brain functions and the development of diseases. Indeed, it has been established that microglia, astrocytes, oligodendrocytes, and NG2 glia influence disease progression. Microglia, initially involved in the clearance of amyloid-beta (Aβ) plaques, can also contribute to neuronal damage by inducing synapse loss, potentially through complement-dependent pathways. Similarly, astrocytes, which typically support neuronal health, can exacerbate excitotoxicity and oxidative stress when their homeostatic function is disrupted. The emergence of activated astrocytes occurs early in the pathophysiology of AD, exhibiting imbalances in neurotransmitter homeostasis, astroglial atrophy, disruptions in synaptic associations, neuroinflammation, and ultimately neurodegeneration.[30]

6.1. Microglia

Microglia, of mesodermal origin, are part of the innate immune system and are responsible for immune surveillance to eliminate agents recognized as foreign. They have phagocytic capacity and trigger inflammatory and repair processes to restore tissue integrity after various types of injury.[31] Microglial cells are characterized by different states of polarization: at one extreme, the M1 phenotype, induced, for example, by the inflammatory agent LPS (lipopolysaccharide obtained from the cell wall of Gram-negative bacteria), which promotes the production of pro-inflammatory cytokines such as IL-1β and TNF-α, and chemokines capable of recruiting other microglial cells, amplifying inflammatory processes. At the other extreme there is the alternative M2 phenotype, associated with the production of anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β, which are involved in repair processes and the fight against neuroinflammation.[32] Between these two extremes, there are intermediate degrees of polarization that characterize the various stages of the pathology. The different phenotypes are associated with morphological changes: resting microglia have a small soma with long ramifications that perceive changes in the surrounding microenvironment; microglia activated by an inflammatory stimulus increase in size, assuming an amoeboid morphology.[33] The accumulation of amyloid aggregates activates microglia, polarizing them toward an M1 phenotype, triggering chronic inflammation that causes cytotoxicity, apoptosis, autophagy dysfunction, increased oxidative stress, neuroinflammation, and brain atrophy.[34]

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[30] H. Hirbec, N. Déglon, L.C. Foo *et al.*, *Emerging technologies to study glial cells,* in *Glia,* 68, 2020, 1692-1728.

[31] X. Kang, J. Tian, Q. Shu *et al.*, *Microglia-neuron crosstalk in Alzheimer's disease: an exploration of molecular mechanisms and pathological implications,* in *Neuroscience,* 583, 2025, 1-9.

[32] H.S. Kwon, S.H. Koh, *Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes,* in *Translational Neurodegeneration,* 9, 2020, 2.

[33] H. Kettenmann, F. Kirchhoff, A. Verkhratsky, *Microglia: new roles for the synaptic stripper,* in *Neuron,* 77, 2013.

[34] V. Lachance, Q. Wang, E. Sweet, I. Choi, C.Z. Cai, X.X. Zhuang, Y. Zhang, J.L. Jiang, R.D. Blitzer, O. Bozdagi-Gunal, B. Zhang, J.H. Lu *et al.*, *Autophagy protein NRBF2 has reduced expression in Alzheimer's brains and modulates memory and amyloid-beta homeostasis in mice,* in *Molecular Neurodegeneration,* 14, 2019, 43. T. Ichimiya, T. Yamakawa, T. Hirano *et al.*, *Autophagy and Autophagy-Related Diseases: A Review,* in *International Journal of Molecular Science,* 21, 2020, 8974. Z. Valiukas, K. Tangalakis, V. Apostolopoulos *et al.*, *Microglial activation states and their implications for Alzheimer's Disease,* in *The Journal of Prevention of Alzheimer's Disease,* 12, 2025, 100013.

Pro-inflammatory mediators such as IL-1β and TNF-α may contribute to hypothalamic dysfunction, impaired neurogenesis, and cognitive decline.[35] Another process that manifests in AD progression is mitochondrial dysfunction, a key process underlying AD pathology, in which mitophagy (or selective degradation of mitochondria by autophagy) and autophagic pathways are altered.[36]

6.2. Macroglia

Macroglia, characterized by larger cells of ectodermal origin, are composed of astrocytes and oligodendrocytes, the former implicated in the formation of the blood-brain barrier, the latter in the formation of the myelin sheath. Recent studies have identified subpopulations of these cell types, differing in morphology and function. Aβ aggregates interact with Toll-like receptors (TLRs) and the NRLP3 inflammasome, increasing astrogliosis and the release of pro-inflammatory cytokines such as TNF-α and IL-1β.[37] Furthermore, Aβ deposition also contributes to BBB damage, making it more permeable to harmful substances, and can also induce the release of inflammatory cytokines and chemokines, thus contributing to chronic neuroinflammation.[38]

6.3. Astrocytes

Reactive astrocytes alter clearance processes, resulting in increased Aβ peptide and the release of pro-inflammatory cytokines and oxidants, exacerbating neuroinflammation and oxidative stress. Astrocytes are essential for Aβ clearance across the BBB, mediated by the LRP1 receptor,[39] while RAGE promotes amyloid influx from the bloodstream into the CNS.[40]

6.4. Oligodendrocytes

Oligodendrocyte progenitor cells (OPCs) are identified by their cell-surface neuronal marker NG2, also known as NG2 glia.[41] These glial cells express APP and the enzyme BACE1, critical components of the amyloidogenic pathway. Aβ leads to the generation of ceramide, which induces mitochondrial dysfunction, oxidative stress, and apoptosis; the damage to oligodendrocytes leads to morphological changes such as cell body shrinkage, increased lactate dehydrogenase release, and reduced metabolic activity. In

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[35] B. PENKE, M. SZŰCS, F. BOGÁR. *New Pathways Identify Novel Drug Targets for the Prevention and Treatment of Alzheimer's Disease. International Journal of Molecular Sciences.* 24, 2023, 5383.

[36] S.N. RAI, C. SINGH, A. SINGH *et al., Mitochondrial Dysfunction: A Potential Therapeutic Target to Treat Alzheimer's Disease,* in *Molecular Neurobiology,* 57, 2020, 3075–3088.

[37] D.V. HANSEN, J.E. HANSON, M. SHENG, *Microglia in Alzheimer's diseas,* in. *Journal of Cell Biology*, 217, 2018, 459-472.

[38] B. PENKE, M. SZŰCS, F. BOGÁR, *New Pathways Identify Novel Drug Targets for the Prevention and Treatment of Alzheimer's Disease*, in *International Journal of Molecular Sciences,* 24, 2023, 5383

[39] W. LI, C. CHEN, B. XU *et al*., *The LDL Receptor-Related Protein 1: Mechanisms and roles in promoting Aß efflux transporter in Alzheimer's disease,* in *Biochemical Pharmacology,* 231, 2025, 116643.

[40] R. BUSINARO, S. LEONE, C. FABRIZI *et al*., *S100B protects LAN-5 neuroblastoma cells against Abeta amyloid-induced neurotoxicity via RAGE engagement at low doses but increases Abeta amyloid neurotoxicity at high doses,* in *Journal of Neuroscience Research,* 83, 2006, 897-906. Z. CAI, N. LIU, C. WANG *et al*., *Role of RAGE in Alzheimer's Disease*, in *Cellular and Molecular Neurobiology,* 36, 2016, 483-95.

[41] J. YANG, X. CHENG, J. QI *et al*., *EGF Enhances Oligodendrogenesis from Glial Progenitor Cells*, in *Frontiers in Molecular Neurosciences,* 10, 2017, 106.

AD, OPC dysfunction leads to active myelin degeneration and reduced repair capacity, resulting in progressive axonal dysfunction and neurodegeneration.

6.5. Glial Cell Crosstalk

The sustained release of pro-inflammatory cytokines accelerates Aβ production and impairs the ability of glial cells to clear and phagocytose Aβ. The interaction between microglia, astrocytes, and oligodendrocytes induces AD progression by amplifying neuroinflammation and neurodegeneration. Pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) are largely involved in this crosstalk. The inability of glial cells to clear amyloid plaques due to impaired phagocytosis significantly contributes to neural loss in AD.[42] Activated astrocytes, stimulated by Aβ plaques and tau aggregates, secrete TNF-α and IL-6, and chemokines such as CCL2 (MCP-1) and CXCL10, which interact with various receptors on the surface of microglia. Microglia are hyperstimulated and trigger neuroinflammatory pathways, promoting neurodegeneration.[43] Microglia and astrocytes generate ROS, including superoxide anion and nitric oxide (NO), thus intensifying oxidative stress.[44]
Activated microglia also release high levels of C1q, causing chronic inflammation and neuronal damage.
In addition to these pro-inflammatory signals, astrocytes and microglia also release anti-inflammatory mediators, including transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), to mitigate and regulate the inflammatory response. However, in AD, this repair process is often insufficient, shifting the balance toward chronic inflammation. Astrocytes and microglia also produce neurotrophic factors such as BDNF and glial cell-derived neurotrophic factor (GDNF). A reduction in these factors in AD further compromises neuronal survival.[45]

7. Risk Factors

7.1. Exposome

The fundamental role of environmental factors, including diet, lifestyle, head trauma, toxins, and others[46] in modulating the risk and progression of AD has been established. The exposome, which encom-

[42] C. Pomilio, R.M. Gorojod, M. Riudavets *et al.*, *Microglial autophagy is impaired by prolonged exposure to β-amyloid peptides: evidence from experimental models and Alzheimer's disease patient,* in *Geroscience,* 42, 2020, 613-63. K. Clayton, J.C. Delpech, S. Herron *et al.*, *Plaque associated microglia hyper-secrete extracellular vesicles and accelerate tau propagation in a humanized APP mouse model,* in *Molecular Neurodegeneration,* 16, 2021, 18.
[43] M. Sil, N. Mukherjee, I. Chatterjee *et al.*, *Glial Cells in Alzheimer's Disease: Pathogenic Mechanisms and Therapeutic Frontiers*, in *Journal of Molecular Neurosciences,* 75, 2025, 87. M. Azmal, J.K. Paul, F.S. Prima *et al.*, *Microglial dysfunction in Alzheimer's disease: Mechanisms, emerging therapies, and future directions,* in *Experimental Neurology,* 392, 2025, 115374.
[44] A. Vilalta, Y. Zhou, J. Sevalle *et al.*, *Wild-type sTREM2 blocks Aβ aggregation and neurotoxicity, but the Alzheimer's R47H mutant increases Aβ aggregation*, in *Journal of Biological Chemistry*, 296, 2021, 100631. C.F. Tsai, G.W. Chen, Y.C. Chen *et al.*, *Regulatory Effects of Quercetin on M1/M2 Macrophage Polarization and Oxidative/Antioxidative Balance,* in *Nutrients*, 14, 2021, 67.
[45] H. Park, M. Ni, Y. Le, *Neuroinflammation and nutrition in Alzheimer's disease,* in *Frontiers in Neurology,* 1, 2025, 1622571.
[46] F. Ippoliti, P. Corbosiero, N. Canitano *et al.*, *Work-related Stress, over nutrition and cognitive disability,* in *Clinica Terapeutica,* 168, 2017, 42-47. P. Ricci, F. Massoni, L. Ricci *et al.*, *Quality of life in dementia sufferers: The role of diet*

passes all environmental exposures throughout an individual's lifetime, provides fundamental insights into the complex etiology of AD.[47] The fact that many of the comorbidities associated with AD are linked to dysregulated metabolic pathways suggests that lifestyle variables, particularly diet, play a role in the etiology of AD. In this sense, lifestyle changes such as physical exercise and diet can interact with inherited susceptibility genes to improve cognitive abilities in AD patients,[48] underlining their relevance for CNS homeostasis, so much so that we now speak of a 'neural exposome'[49] which includes a whole series of environmental factors, of different kinds, ranging from air pollution and dietary habits to occupational exposures and psychosocial stresses – which impact the physiological balance of the CNS.[50]

A relationship between education level and amyloid accumulation has also been identified: a higher level of education is associated with greater amyloid deposition in individuals with MCI, but with a reduced amyloid burden in those with AD. This pattern supports the cognitive reserve hypothesis, according to which education can strengthen compensatory neural mechanisms, delaying the clinical onset of dementia symptoms.[51] Loneliness has been shown to significantly contribute to cognitive impairment and dementia in older adults. Social isolation and loneliness (perceived social isolation) are considered risk factors for the development of dementia in the elderly population.[52] In this regard, the development of innovative treatments and the promotion of interventions aimed at promoting a healthy lifestyle are essential to improve the lives of people affected by AD.[53]

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and exercise, in *Current Alzheimer Research,* 15, 2018, 400-407. C.E. Finch, A.M. Kulminski, *The Alzheimer's Disease Exposome,* in *Alzheimer's Dementia,* 15, 2019, 1123–1132. N. Soldevila-Domenech, A. Ayala-Garcia, M. Barbera *et al.*, *Adherence and intensity in multimodal lifestyle-based interventions for cognitive decline prevention: state-of-the-art and future directions,* in *Alzheimer's Research and Therapeutics,* 17, 2025, 61. M.A. Kareem, A. Ashwini, T. Sunil, *The Role of the Exposome in Aging and Age-Related Diseases: A Comprehensive Review*, in *Journal of Pharmacy and Bioallied Sciences*, 17(1), 2025, S2-S5.

[47] M. Monaco, C. Torazza, E. Fedele *et al.*, *The Impact of the Exposome on Alzheimer's Disease: The Influence of Nutrition,* in *International Journal of Molecular Sciences,* 26, 2025, 3015.

[48] C.E. Finch, A.M. Kulminski, *The Alzheimer's Disease Exposome,* in *Alzheimer's Dementia,* 15, 2019, 1123–1132. F. Galkin, O. Kovalchuk, D. Koldasbayeva *et al.*, *Stress, Diet, Exercise: Common Environmental Factors and Their Impact on Epigenetic Age,* in *Ageing Research Reviews*, 88, 2023, 101956. L. Yang, Z. Yuan, C. Peng, *Effects of Aerobic Exercise on Cognitive Function and Quality of Life in Patients with Alzheimer's Disease: A Systematic a systematic review and meta-analysis,* in *BMJ Open,* 15, 2025.

[49] R. Granov, S. Vedad, S.H. Wang *et al.*, *The Role of the Neural Exposome as a Novel Strategy To Identify and Mitigate Health Inequities in Alzheimer's Disease and Related Dementias,* in *Molecular Neurobiology,* 62, 2025, 1205–1224.

[50] R. Vermeulen, E.L. Schymanski, A.L. Barabsi *et al.*, *The Exposome and Health: Where Chemistry Meets Biology*, in *Science,* 367, 2020, 392–396.

F. Sedghi, E. Foroughi, F. Sheikhzadeh *et al.*, *Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: A meta-analysis,* in *IBRO Neuroscience Reports,* 19, 2025, 133-142.

[51] R.H. Aunsmo, B.H.Strand, S. Bergh *et al.*, *Loneliness trajectories and dementia risk: Insights from the HUNT cohort study,* in *Alzheimer's Dementia (Amst),* 17, 2025, e70154.

[52] W. Araki, *Social Isolation as a Risk Factor for Dementia: Insights from Animal Model Studies,* in *Current Alzheimer Research,* 22, 2025, 165-173.

[53] Y.L. Zhao, Y.N. Hao, Y.J. Ge *et al.*, *Variables Associated with Cognitive Function: An Exposome-Wide and Mendelian Randomization Analysis,* in *Alzheimer's Research and Therapeutics,* 17, 2025, 13.

7.2. Immunosenescence

An emerging key factor contributing to the decline in brain organization and function is cellular senescence, characterized at the genomic level by stable cell cycle arrest, primarily driven by the p16INK4a/Rb and p21CIP1/p53 pathways, accompanied by macromolecular and metabolic alterations associated with a pro-inflammatory hypersecretory phenotype known as senescence-associated secretory phenotype (SASP).[54] SASP is characterized by the synthesis of various biologically active molecules, such as inflammatory mediators, growth factors, and extracellular matrix proteins, which can influence the microenvironment, affecting neighboring cells. The process is also characterized by oxidative stress, chromatin remodeling, telomere shortening, accumulation of DNA damage and reactive oxygen species (ROS), lysosomal enlargement, macromolecular breakdown, and metabolic imbalance. The number of senescent cells increases with age, and their involvement has been suggested in the pathogenesis of AD[55] since at the CNS level, glial cells are also affected by a senescence process: microglia become neurotoxic and harmful by producing inflammatory cytokines, superoxide anions and nitric oxide, promoting the phenomenon of 'oxi-inflamm-aging'. Senescent astrocytes promote inflammation through SASP factors.[56] Indeed, several SASP factors, including MMP-3, IL-1α, IL-6 and IL-8, are increased in the brains of PD and AD patients, indicating that senescent cells could contribute to neurodegeneration.[57] Therefore, eliminating senescent cells within the CNS, or at least delaying their senescence, and mitigating the adverse effects of widespread SASP have been identified as targets for the prophylaxis and adjunctive treatment of neurodegenerative diseases.

7.3. Obesity

Overnutrition, resulting from excess caloric intake, directly contributes to overweight and obesity. Eating habits and nutrient intake can have a profound impact on the body's resilience to various stressors. Stress is one of the main factors inducing the development of visceral fat associated with obesity. Overweight and obesity are responsible for the development of chronic low-grade inflammation and represent one, if not the main, modifiable risk factor, as dietary changes can modulate the risk of developing AD and subsequently disease progression.[58] Numerous studies have established a correlation between obesity and dementia, and AD has been described as a metabolic disease or type 3 diabetes, influenced

[54] Q. Zhang, G. Yang, Y. Luo *et al*., *Neuroinflammation in Alzheimer's Disease: Insights from Peripheral Immune Cells,* in *Immunity and Ageing,* 21, 2024, 38.

[55] S. Ristori, G. Bertoni, E. Bientinesi *et al., The Role of Nutraceuticals and Functional Foods in Mitigating Cellular Senescence and Its Related Aspects: A Key Strategy for Delaying or Preventing Aging and Neurodegenerative Disorders,* in *Nutrients,* 17, 2025, 1837.

[56] K. Simmnacher, F, Krach, Y. Schneider *et al*., *Unique Signatures of Stress-Induced Senescent Human Astrocytes,* in *Experimental Neurology*, 334, 2020, 113466.

[57] W.Y. Wang, M.S. Tan, J.T. Yu *et al*., *Role of Pro-Inflammatory Cytokines Released from Microglia in Alzheimer's Disease*, in *Annals of Translational Medicine,* 3, 2015, 36.

Z. Si, L. Sun, X. Wang, *Evidence and Perspectives of Cell Senescence in Neurodegenerative Diseases*, in *Biomedicine and Pharmacotherapy*, 137, 2021, 111327.

[58] D. Khanna, S. Khanna, P. Khanna *et al., Obesity: A Chronic Low-Grade Inflammation and Its Markers*, in *Cureus,* 14, 2022, 22711.

Y. Dhurandhar, S. Tomar, A. Das *et al*., *Chronic inflammation in obesity and neurodegenerative diseases: exploring the link in disease onset and progression*, in *Molecular Biology Reports,* 52, 2025,424.

by the development of hypertrophic adipose tissue with the release of proinflammatory adipokines and various mechanisms of leptin and insulin resistance.[59] Adipose tissue is currently considered an active endocrine organ, producing important mediators involved in the regulation of metabolism and inflammatory mechanisms. Insulin and leptin resistance have been linked to dysregulation of energy balance and the induction of a chronic inflammatory state, important cofactors in cognitive impairment and the onset and progression of AD.[60] Obesity is associated with dysregulated leptin secretion due to adipose tissue dysfunction, contributing to metabolic abnormalities and hippocampal synaptic disorders, factors that increase the risk of comorbidities, cognitive decline, and neurodegenerative diseases. Furthermore, obesity increases inflammatory molecules such as RAGE, cytokines (IL-6 and TNF-α), leptin, insulin, and free fatty acids, which disrupt the degradation of β-amyloid peptide and promote its accumulation in the brain.[61] The elevated leptin levels observed in obese individuals lead to leptin resistance in the brain. Signal transduction and communication between adipokines secreted by adipose tissue and the central nervous system have an increasingly recognized role in metabolic and neurological regulation. This action contributes to the vulnerability of obese individuals to the development of cognitive impairment.[62]

8. Nutraceuticals

Growing interest is focusing on nutraceuticals and functional foods as potential modulators of cellular senescence, potentially influencing the development of neurodegenerative diseases.[63] Various natural compounds, known as 'bioactive compounds', present in foods can interact with biological processes to provide benefits and because of this they have been included in a new class of compounds called 'nutraceuticals' (a crasis between the words 'nutrients' and 'pharmaceuticals').[64] A growing body of evidence suggests that nutraceuticals and whole-food dietary approaches can influence brain health and cognitive function, offering a promising avenue for intervention.[65] Several bioactive compounds function as epigenetic modulators, influencing gene expression, chromatin organization, DNA methylation patterns, and noncoding RNA expression, and both diet quality and quantity epigenetically modulate DNA

[59] S.M. De La Monte, *Type 3 diabetes is sporadic Alzheimer's disease: mini-review,* in *European Neuropsychopharmacology*, 24, 2014, 1954-60. M. Kciuk, W. Kruczkowska, J. Gałęziewska *et al.*, *Alzheimer's Disease as Type 3 Diabetes: Understanding the Link and Implications*, in *International Journal of Molecular Sciences,* 25, 2024, 11955.

[60] R. Businaro, F. Ippoliti, S. Ricci *et al.*, *Alzheimer's disease promotion by obesity: induced mechanisms-molecular links and perspectives,* in *Current Gerontology and Geriatric Research,* 2012, 986823.

[61] E.A. Al-Suhaim, A.A. Alrubaish, H.A. Aldossary *et al.*, *Obesity and Cognitive Function: Leptin Role Through Blood-Brain Barrier and Hippocampus,* in *Molecular Neurobiology*, 62, 2025, 16280-16301.

[62] E.A. Al-Suhaim, A.A. Alrubaish, H.A. Aldossary *et al.*, *Obesity and Cognitive Function: Leptin Role Through Blood-Brain Barrier and Hippocampus,* in *Molecular Neurobiology*, 62, 2025, 16280-16301.

[63] S. Ristori, G. Bertoni, E. Bientinesi *et al.*, *The Role of Nutraceuticals and Functional Foods in Mitigating Cellular Senescence and Its Related Aspects: A Key Strategy for Delaying or Preventing Aging and Neurodegenerative Disorders,* in *Nutrients,* 17, 2025, 1837.

[64] H.K. Biesalski, L.O. Dragsted, L. Elmadfa *et al.*, *Bioactive Compounds: Definition and Assessment of Activity,* in *Nutrition, 25*, 2009, 1202–1205.

[65] M.C. Morris, *Nutrition and Risk of Dementia: Overview and Methodological Issues*, in *Annals of the New York Academy of Sciences,* 1367, 2016, 31–37.

methylation and mental health.[66] For example, the presence of antioxidants in fruits and vegetables has been shown to mitigate oxidative stress induced by environmental contaminants[67] and dietary polyphenols showed several benefits in AD, mitigating pathological manifestations in part due to their ability to cross the blood-brain barrier.[68] Neuroprotective effects vary depending on the nutrient used and may include a reduction in neuroinflammation, activation of the endogenous antioxidant defense system, and modulation of the structure and function of the gut microbiota.[69] Supplementation of essential nutrients, such as long-chain polyunsaturated fatty acids, vitamin E, and minerals, can minimize inflammation, enhance antioxidant defenses, and reduce the risk and incidence of age-related diseases, such as cardiovascular disease and neurodegenerative diseases. Dietary supplementation strategies have been shown to be effective in subjects with mild cognitive impairment, while weaker results have been obtained in patients with advanced neurodegenerative diseases. Additional supplementation has also been shown to improve depression, which is of considerable benefit considering the comorbidity between cognitive impairment/dementia and depression.[70] Natural antioxidant and anti-inflammatory compounds found in plant-based foods, such as fruits, particularly berries (such as strawberries, blueberries, blackcurrants, blackberries, cranberries, and mulberries), exert neuroprotective activity.[71] Specifically, in the presence of hydroalcoholic extracts obtained from blueberries, the mRNA expression of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α decreased, as did the expression of iNOS, while that of Arg-1 increased, markers of pro- and anti-inflammatory phenotypes, respectively. It has been shown that during the inflammatory response, blueberry extract shifts M1 polarization toward the M2 phenotype.[72] A pilot study in obese/overweight patients with metabolic syndrome demonstrated that significant changes in cytokine gene expression levels were observed after the intake of high-fat/high glycemic load meals enriched with blueberries. In particular, the mRNA expression of IL-6 and TGF-β, pro- and anti-inflammatory cytokines, respectively, was significantly decreased and increased after blueberry supplementation, indicating a positive impact of blueberry ingestion in reducing the risk of inflammation.[73] Curcumin, a polyphenolic compound derived from Curcuma longa, has attracted considerable attention

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[66] R.A. Bekdash, E*pigenetics, Nutrition, and the Brain: Improving Mental Health through Diet*, in *International Journal of Molecular Sciences, 25*, 2024, 4036.

[67] R.L. Prior, *Fruits and Vegetables in the Prevention of Cellular Oxidative Damage,* in *The American Journal of Clinical Nutrition, 78*, 2003, 570S–578S. M.M. Rahaman, R. Hossain, J. Herrera-Bravo *et al.*, *Natural antioxidants from some fruits, seeds, foods, natural products, and associated health benefits: An update,* in *Food Science and Nutrition,* 11, 2023, 1657-1670.

[68] D. Vauzour, A. Rodriguez-Mateos, G. Corona *et al.*, *Polyphenols and Human Health Prevention of Disease and Mechanisms of Action,* in *Nutrients*, 2, 2010, 1106–1131.

[69] C. Angeloni, R. Businaro, D. Vauzour, *The role of diet in preventing and reducing cognitive decline,* in *Current Opinion in Psychiatry,* 33, 2020, 432-438.

[70] R. Businaro, D. Vauzour, J. Sarris *et al.*, *Therapeutic Opportunities for Food Supplements in Neurodegenerative Disease and Depression,* in *Frontiers in Nutrition*, 8, 2021, 669846.

[71] R. Businaro, M. Corsi, R. Asprino *et al.*, *Modulation of Inflammation as a Way of Delaying Alzheimer's Disease Progression: The Diet's Role,* in *Current Alzheimer Research,* 15, 2018, 363-380.

[72] M.G. De Caris, M. Grieco, E. Maggi *et al.*, *Blueberry Counteracts BV-2 Microglia Morphological and Functional Switch after LPS Challenge,* in *Nutrients,* 12, 2020, 1830. S.M. De La Monte, *Type 3 diabetes is sporadic Alzheimer's disease: mini-review,* in *European Neuropsychopharmacology,* 24, 2014, 1954-60.

[73] A.P. Sobolev, A. Ciampa, C. Ingallina *et al.*, *Blueberry-Based Meals for Obese Patients with Metabolic Syndrome: A Multidisciplinary Metabolomic Pilot Study*, in *Metabolites,* 9, 2019, 138.

for its potential therapeutic benefits, particularly in combating inflammation, oxidative stress, and metabolic disorders. Its chemical structure, characterized by conjugated double bonds between two aromatic rings, allows it to act as an electron donor, thus mitigating the formation of free radicals. Curcumin's anti-inflammatory properties are related to the inhibition of the NF-κB pathway, resulting in the reduction of inflammatory markers in adipocytes and macrophages. Furthermore, curcumin modulates oxidative stress by activating the NRF2 pathway, enhancing the cell's antioxidant defenses.[74]

Furthermore, the ancient durum wheat variety Senatore Cappelli was analyzed at four stages of the food chain (seeds, flour, pasta, and chaff) by NMR spectroscopy, revealing the presence of bioactive molecules such as phenolic acids and carotenoids. The hydroalcoholic extracts obtained from the components of the chain showed the ability to polarize microglial cells towards an anti-inflammatory phenotype, even after the addition of LPS. An antioxidant response was detected in both microglia and the nematode Caenorhabditis elegans, where the extracts also implemented an anti-stress resilience response, stimulated innate immunity, and were able to extend lifespan, indicating potential anti-aging and pro-longevity properties. These results position the ancient wheat Senatore Cappelli as a valuable resource for the enhancement of bioactive compounds, supporting its reintroduction into modern diets and its use in the development of functional foods.[75]

The 36-month LipiDiDiet study demonstrated that a multinutrient intervention slowed cognitive decline and brain atrophy and improved memory performance in individuals with prodromal AD, thus highlighting the role of diet in modifying AD risk.[76]

Both the ketogenic diet (KD) and the Mediterranean diet have been shown to exert anti-inflammatory effects by reducing the expression of pro-inflammatory cytokines, decreasing microglial activation, and restoring the integrity of the blood-brain barrier.[77] The primary activity of the ketogenic diet has been linked to improved mitochondrial function and reduced oxidative stress. β-Hydroxybutyrate, the most studied ketone body, has been shown to reduce the production of reactive oxygen species (ROS) by improving mitochondrial respiration: stimulating the cellular endogenous antioxidant system with the activation of nuclear factor erythroid-derived factor 2-related (Nrf2), modulating the ratio between the oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD^+/NADH), and increasing the efficiency of the electron transport chain through the expression of uncoupling proteins. Furthermore, the ketogenic diet exerts anti-inflammatory activity by inhibiting the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the inflammasome, as well as by inhibiting histone

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[74] M. Cerullo, F. Armeli, B. Mengoni *et al.*, *Curcumin Modulation of the Gut-Brain Axis for Neuroinflammation and Metabolic Disorders Prevention and Treatment,* in *Nutrients,* 17, 2025, 1430.

[75] G. Vinci, S.A. Prencipe, F. Armeli *et al.*, *A Multimethodological Approach for the Valorization of "Senatore Cappelli" Wheat Milling By-Products as a Source of Bioactive Compounds and Nutraceutical Activity,* in *International Journal of Environmental Research and Public Healt*h, 20, 2023, 5057.

F. Armeli, M. Beccaccioli, S.A. Prencipe *et al.*, *Bioactive molecules in wheat "Senatore Cappelli" food chain: Extraction, analysis, processing, and beneficial properties*, in *Food and Chemical Toxicology*, 201, 2025,115475.

B. Mengoni, F. Armeli, E. Schifano *et al.*, *In Vitro and In Vivo Antioxidant and Immune Stimulation Activity of Wheat Product Extracts,* in *Nutrients,* 17, 2025, 302.

[76] H. Soininen, A. Solomon, P.J. VISSER *et al.*, *36-Month LipiDiDiet Multinutrient Clinical Trial in Prodromal Alzheimer's Disease,* in *Alzheimer's Dementia,* 17, 2021, 29–40.

[77] M. Monaco, C. Torazza, E. Fedele *et al.*, *The Impact of the Exposome on Alzheimer's Disease: The Influence of Nutrition*, in *International Journal of Molecular Sciences,* 26, 2025, 3015.

deacetylases (HDACs), enhancing memory encoding.[78] Similarly, the Mediterranean diet, rich in antioxidants, reduces postprandial levels of hydrogen peroxide and lipid peroxides.[79] In particular, polyphenols, abundant in this diet, combat neuroinflammation by reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and inhibiting the NF-κB pathway.[80] Their antioxidant properties neutralize ROS, enhance antioxidant enzymes, strengthen the blood-brain barrier, and modulate the gut microbiota, all contributing to neuroprotection. A recent study confirms the link between an anti-inflammatory diet and the decreased risk to develop neurodegenerative diseases.[81]

9. Gut-Brain Axis: New Therapeutic Strategies with Probiotic Administration

Recent studies have highlighted the central role of the gut microbiota in maintaining homeostasis and preventing CNS imbalances.[82] Some inflammatory diseases, including AD, share alterations in the gut microbiome and immune pathways that have been associated with disease progression.[83]

The intestine, especially the colon, hosts numerous microorganisms, including approximately 1,000 bacterial species and 7,000 strains, with a predominance of Firmicutes and Bacteroidetes, as well as yeasts and viruses,[84] collectively referred to as the microbiota. Under physiological conditions, this set of microorganisms promote health by regulating metabolism, breaking down complex dietary polysaccharides, modulating intestinal motility, strengthening the intestinal barrier, and influencing fat distribution and immune function. Through the gut-brain axis, the gut microbiota can indirectly modulate CNS function by producing immune activators, neurotransmitters, neuromodulators, and endocrine factors that can cross the blood-brain barrier or communicate through neural pathways.[85] Some microbial metabolites, such as lipopolysaccharides and short-chain fatty acids, can compromise the integrity of the blood-brain barrier, facilitating neuroinflammation and neuronal damage, as has been demonstrated in cases of dysbiosis (alteration in the number and types of microorganisms that make up the host's microbiota). It is important to note that the composition of the gut microbiota can be influenced by diet, lifestyle, and even environmental factors, with alterations in microbiota diversity often resulting in various neuro-

[78] A. Pinto, A. Bonucci, E. Maggi *et al.*, *Anti-Oxidant and Anti-Inflammatory Activity of Ketogenic Diet: New Perspectives for Neuroprotection in Alzheimer's Disease,* in *Antioxidants (Basel),* 7, 2018, 63.

[79] E.M. Yubero-Serrano, A. Garcia-Rios, J. Delgado-Lista *et al.*, *Postprandial Effects of the Mediterranean Diet on Oxidant and Antioxidant Status in Elderly Men and Women*, in *Journal of the American Geriatrics Society,* 59, 2011, 938–940.

[80] I. Grabska-Kobyłecka, P. Szpakowski, A. Król *et al.*, *Polyphenols and Their Impact on the Prevention of Neurodegenerative Diseases and Development,* in *Nutrients,* 15, 2023, 3454.

[81] D.M. Van Lent, H.G. Mesa, M.I. Short *et al.*, *Association between Dietary Inflammatory Index Score and Incident Dementia,* in *Alzheimer's Dementia,* 21, 2025, 14390.

[82] W. Lei, Y. Cheng, X. Liu *et al.*, *Gut microbiota-driven neuroinflammation in Alzheimer's disease: from mechanisms to therapeutic opportunities,* in *Frontiers in Immunology,* 16, 2025, 1582119.

[83] M. Luca, M. Di Mauro, M. Di Mauro *et al.*, *Gut microbiota in Alzheimer's disease, depression, and type 2 diabetes mellitus: the role of oxidative stress*, in *Oxidative Medicine and Cellular Longevity*, 2019, 4730539.

[84] W. Liu, J. Guo, Y. Dong *et al.*, *Efficacy of probiotic supplementation in influencing cognitive function in Alzheimer's disease: A systematic review and meta-analysis,* in *Journal of Food Science*, 90, 2025, 70037.

[85] J.F. Cryan, K.J. O'riordan, C.S.M. Cowan *et al.*, *The Microbiota-Gut-Brain Axis,* in *Physiological Reviews,* 99, 2019, 1877-2013.

T.G. Dinan, J.F. Cryan, *Gut-brain axis in 2016: Brain-gut-microbiota axis - mood, metabolism and behaviour*, in *Nature Reviews Gastroenterology and Hepatology*, 14, 2017, 69-70.

logical and psychiatric disorders. Dysbiosis can lead to increased intestinal permeability, a condition often referred to as 'leaky gut'. This allows harmful substances to enter the bloodstream, triggering systemic inflammation, which can then affect brain function. There is growing evidence that the gut microbiota plays a significant role in modulating brain function, primarily through the production of specific metabolites. Some bacteria, such as Bacillus subtilis and Escherichia coli, produce amyloid-like proteins, which can penetrate the intestinal barrier, enter the bloodstream, and potentially contribute to neurodegenerative processes.[86]

Long-term use of broad-spectrum antibiotics has been associated with alterations in the composition of the gut microbiota, resulting in cognitive impairment and an increased risk of developing Alzheimer's disease.[87]

Patients with AD have lower gut microbial diversity, characterized by an increase in pro-inflammatory bacteria and a decrease in beneficial species.[88] Furthermore, differences in microbiota composition are observed between patients with mild cognitive impairment (MCI) and those with advanced AD, indicating a gradual shift in the microbiota as the disease progresses.[89] Dysbiosis is believed to contribute to early AD pathology by promoting immune aging, cytokine imbalances, and neuroinflammation.[90] The promotion of neurodegenerative disorders, also induced by systemic inflammation, has been linked to a decrease in bacterial strains capable of producing short-chain fatty acids such as butyrate. Butyrate, along with other ketone bodies, is able to cross the BBB and replace the energy functions of glucose in situations of glucose deficiency. Reduced production of SCFAs leads to the accumulation of amyloid plaques, metabolic dysfunction, and microglial deterioration, all of which accelerate cognitive decline.[91] Furthermore, the decline in butyrate-producing bacteria is often accompanied by an increase in pro-inflammatory bacteria, triggering both local and systemic inflammation, further exacerbating neuroinflammation.[92] The results of these studies have led to the hypothesis that modulating the gut microbiome could offer potential therapeutic strategies to improve the treatment of neurodegenerative diseases.[93] Furthermore, reduced gut microbiota diversity can alter tryptophan and serotonin levels, influencing the production of critical molecules such as dopamine and brain-derived neurotrophic factor

[86] R.P. Friedland, M.R. Chapman, *The role of microbial amyloid in neurodegeneration*, in *PLoS Pathogens,* 13, 2017, 1006654.

[87] F. Angelucci, K. Cechova, J. Amlerova *et al*., *Antibiotics, gut microbiota, and Alzheimer's disease,* in *Journal of Neuroinflammation,* 16, 2019, 108. M.R. Minter, R. Hinterleitner, M. Meisel *et al*., *Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged $APP_{SWE}/PS1_{\Delta E9}$ murine model of Alzheimer's disease,* in *Scientific Reports,* 7, 2017, 10411.

[88] N.M. Vogt, R.L. Kerby, K.A. Dill-Mcfarland *et al*., *Gut microbiome alterations in Alzheimer's disease,* in *Scientific Reports,* 7, 2017, 13537.

[89] P. Liu, L. Wu, G. Peng *et al*., *Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort,* in *Brain, Behavior and Immunity,* 80, 2019, 633–43.

[90] H. Li, J. Ni, H. Qing, *Gut Microbiota: Critical Controller and Intervention Target in Brain Aging and Cognitive Impairment,* in *Frontiers in Aging Neuroscience,* 13, 2021, 671142.

[91] T.J. Wenzel, E.J. Gates, A.L. Ranger *et al*., *Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells,* in *Molecular and Cellular Neuroscience,* 105, 2020, 103493

[92] J.P. Haran, S.K. Bhattarai, S.E. Foley *et al*., *Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway,* in *mBio journal,* 10, 2019, 00632–00619.

[93] W. Liu, J. Guo, Y. Dong *et al*., *Efficacy of probiotic supplementation in influencing cognitive function in Alzheimer's disease: A systematic review and meta-analysis*, in *Journal of Food Science,* 90, 2025.

(BDNF).[94] Various strategies have been developed to shift the microbiota composition toward neuroprotective species, such as the administration of probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT). Probiotics are live microorganisms that can significantly contribute to mitigating inflammatory processes by acting on the gut-brain axis, reducing the release of inflammatory mediators, and counteracting oxidative stress.[95] Lactobacilli species have demonstrated benefits in aging by improving immunity and maintaining the balance of the gut microbiota. With some preclinical studies, we have demonstrated that the yeast Milmed, obtained from S. cerevisiae after exposure to millimeter-wavelength electromagnetic radiation, reverses pro-inflammatory M1-polarized microglia to an anti-inflammatory phenotype, as demonstrated morphologically by the recovery of the quiescent phenotype by microglia, by the decrease in IL-1β, IL-6, TNF-α mRNAs, and by the decreased expression of iNOS. Furthermore, Milmed induced the secretion of IL-10 and the expression of Arginase-1, cellular markers of anti-inflammatory-polarized M2 microglia. These data suggest that Milmed can be considered a probiotic with diversified anti-inflammatory activity, capable of directing the polarization of microglial cells.[96] Treatment with Milmed cultured yeast or its dried powder promoted autophagic flux, as demonstrated by increased expression of Beclin-1, ATG7, LC3, and p62 mRNAs and by inhibition of mTOR. It also enhanced the antioxidant response by increasing the expression of NRF2, SOD1, and GPX. Dietary supplementation with Milmed prolonged the survival of C. elegans and reduced age-related ROS accumulation. The pro-longevity effect was dependent on SKN-1/Nrf2 activation, as demonstrated by the lack of benefit in skn-1 mutants. Thus, Milmed yeast demonstrated significant pro-autophagy and antioxidant activity with significant pro-longevity effects in C. elegans, thus extending its lifespan and improving its resistance to stress. This, combined with the Milmed previously demonstrated anti-inflammatory activity, highlights its role as a highly effective probiotic for its beneficial health effects. Activation of the SKN-1/NRF2 pathway and modulation of autophagy support the therapeutic potential of Milmed in neuroprotection and healthy aging.

Confirming these results, several clinical trials included in a meta-analysis have indicated that probiotic supplementation may improve cognitive function in individuals with mild cognitive impairment (MCI), a prodromal phase of AD.[97]

New therapeutic horizons are emerging thanks to complementary medicines that complement traditional pharmacological treatments. Probiotics, supported by prebiotics, have demonstrated an im-

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[94] G. Morris, M. Berk, A. Carvalho *et al.*, *The Role of the Microbial Metabolites Including Tryptophan Catabolites and Short Chain Fatty Acids in the Pathophysiology of Immune-Inflammatory and Neuroimmune Disease*, in *Molecular Neurobiology,* 54, 2017, 4432-4451. R. Hashemi, M.M.H.M. Raouf, T.S. Salih *et al.*, *Impact of probiotic supplementation on serum levels of brain-derived neurotrophic factor: GRADE-based dose-response meta-analysis,* in *BMC Nutrition,* 11, 2025, 61.

[95] X. Liu, S. Cao, X. Zhang, *Modulation of gut microbiota-brain axis by probiotics, prebiotics, and diet,* in *Journal of Agricultural and Food Chemistry,* 63, 2015, 7885–95.

[96] F. Armeli, B. Mengoni, E. Maggi *et al.*, *Milmed Yeast Alters the LPS-Induced M1 Microglia Cells to Form M2 Anti-Inflammatory Phenotype*, in *Biomedicines*, 10, 2022, 3116.

[97] G. Zhu, J. Zhao, H. Zhang *et al.*, *Probiotics for Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and Meta-Analysis,* in *Foods,* 10, 2021, 1672

W. Liu, J. Guo, Y. Dong *et al.*, *Efficacy of probiotic supplementation in influencing cognitive function in Alzheimer's disease: A systematic review and meta-analysis,* in *Journal of Food Science,* 90, 2025, 70037.

portant role in reducing systemic inflammation and oxidative stress, two essential pathogenetic factors in the promotion of chronic neurodegenerative diseases.