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RELATIONSHIP BETWEEN CHRONIC INFLAMMATION AND ALZHEIMER'S DISEASE

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To my beloved grandmother,
whose battle with Alzheimer's disease inspires this work

Abbreviations

AD: Alzheimer's disease
AMBAR: Alzheimer Management By Albumin Replacement
ApoE: apolipoprotein E
APP: amyloid precursor protein
Aß: amyloid beta
BACE1: ß-secretase-1
BBB: blood-brain barrier
BPSD: behavioral and psychological symptoms of dementia
CDK5: cyclin-dependent kinase 5
CNS: central nervous system
CSF: blood-cerebrospinal fluid
CVOs: circumventricular organs
EMA: European Medicines Agency
ERK: extracellular regulated kinases
FDA: Food and Drug Administration
GSK3ß: glycogen synthase kinase-3ß
JNK: JUN NH2 terminal kinases
LPS: lipopolysaccharide
MAPK: mitogen-activated protein kinase
MCI: mild cognitive impairment
MedDiet: Mediterranean diet
MIND: Mediterranean-DASH intervention for Neurodegenerative Delay diet
NF-kß: Nuclear Factor Kappa ß
NF: nutraceutical formulation
NFTs: neurofibrillary tangles
P38-MAPK: p38 mitogen-activated protein kinase
PA: physical activity
PHF: paired helical filaments
PP2A: protein phosphatase 2A
PPAR-γ: peroxisome proliferator-activated receptors
PVMs: systemic perivascular macrophages
RCTs: randomized clinical trials
SCFAs: short-chain fatty acids
SDG: sustainable development goals
SNPs: single nucleotide polymorphisms
STAT 3: signal transducer and activator of transcription 3
sTREM: extracellular soluble TREM2
T2DM: type 2 diabetes mellitus
Th2: T helper 2
TJs: tight junctions

Abstract

Alzheimer's disease is the most common form of dementia, accounting for 60 to 70% of total cases. It is a multifactorial neurodegenerative disease with devastating consequences for which there is still no cure. Considering the involvement of a chronic inflammatory state in other chronic diseases such as obesity or diabetes, the question arises about a possible relationship between chronic inflammation and Alzheimer's disease.

This review attempts to evaluate, based on current evidence, the knowledge that explains the interaction between the different molecular pathways involved in inflammatory processes that contribute to this chronic inflammatory state. Understanding these interactions is crucial, as proper management of chronic inflammatory processes could open the possibility of developing targeted therapies for Alzheimer's disease.

The literature review was conducted through an exhaustive search of information in databases such as PubMed and Scopus, as well as online journals and books. The sources were meticulously selected to ensure the most relevant and recent studies were included, providing a comprehensive overview of the current state of research in this

Although there is documented evidence of the contribution of chronic inflammation to Alzheimer's disease, further studies and clinical trials are still necessary to fully justify this relationship. Identifying the specific molecular pathways involved in the inflammatory processes would be key to developing promising therapeutic strategies. These future therapies could potentially slow the progression of the disease or even prevent its development, providing hope for millions of patients and their families affected by this condition.

Keywords: Alzheimer's disease, chronic inflammation, molecular pathways, therapeutic strategies.

Resum

La malaltia d'Alzheimer és la forma més comuna de demència, representant del 60 al 70% dels casos totals. És una malaltia neurodegenerativa multifactorial amb conseqüències devastadores per a la qual encara no hi ha cura. Considerant la implicació d'un estat inflamatori crònic en altres malalties cròniques com l'obesitat o la diabetis, sorgeix la qüestió sobre una possible relació entre la inflamació crònica i la malaltia d'Alzheimer.

Aquesta revisió intenta avaluar, basant-se en l'evidència actual, el coneixement que explica la interacció entre les diferents vies moleculars implicades en els processos inflamatoris que contribueixen a aquest estat inflamatori crònic. Entendre aquestes interaccions és crucial, ja que maneig adequat d'aquests processos inflamatoris crònics podria obrir la possibilitat de desenvolupar teràpies dirigides per a la malaltia d'Alzheimer.

La revisió bibliogràfica es va dur a terme mitjançant una cerca exhaustiva d'informació en bases de dades com PubMed i Scopus, a més de revistes i llibres en línia. Les fonts van ser meticulosament seleccionades per assegurar que s'incloguessin els estudis més rellevants i recents, proporcionant una visió integral de l'estat actual de la recerca en aquest camp.

Tot i que hi ha evidència documentada de la contribució de la inflamació crònica a la malaltia d'Alzheimer, encara són necessaris més estudis i assaigs clínics per acabar de justificar aquesta relació. Identificar les vies moleculars específiques implicades en els processos inflamatoris seria clau per desenvolupar estratègies terapèutiques prometedores. Aquestes futures teràpies podrien alentir la progressió de la malaltia o fins i tot prevenir-ne el desenvolupament, oferint esperança a milions de pacients i les seves famílies afectades per condició.

Paraules clau: malaltia d'Alzheimer, inflamació crònica, rutes moleculars, estratègies terapèutiques.

Integration of fields

The main teaching area is **Physiology and Pathophysiology**, as this work focuses on studying the relationship between chronic inflammation and Alzheimer's disease at a pathophysiological level. Specifically, it examines how chronic inflammation may have implications in the development and pathogenesis of neurodegenerative diseases, such as Alzheimer's disease.

As secondary areas, Molecular Nutrition and Pharmacology and Therapeutics are included. Regarding **Molecular Nutrition**, emphasis is placed on studying the different molecular pathways and how they are influenced by chronic inflammation and their possible interaction with Alzheimer's disease.

As for the field of **Pharmacology and Therapeutics**, the current pharmacological treatments for the disease and their challenges are described, noting that none of them prevent its progression. Encouraging pharmacological advances are mentioned, but there is also an emphasis on the search for new therapeutic measures, such as nutritional supplementation or other dietary interventions, which could serve as tools for the prevention and treatment of the disease.

SDG (Sustainable Development Goals)

The population that this project can impact consists of individuals suffering from Alzheimer's disease. Patients with this disease, generally elderly individuals as age is the primary risk factor, experience a decline in their quality of life as the disease progresses, given that current pharmacological treatments only focus on symptom improvement. Furthermore, the constant increase in life expectancy worldwide leads to a higher prevalence of the disease, resulting in more individuals affected and greater related expenses, thereby highlighting the need for effective therapeutic strategies and early diagnosis. This study focuses on the analysis of chronic inflammation and its relationship with Alzheimer's disease, presenting a possible therapeutic strategy for the proper management and prevention of this condition. The ideal objective is to achieve a reduction in prevalence and, consequently, reduce the healthcare, social, and economic burden associated with neurodegenerative diseases.

Therefore, the SDGs included in this project are:

Within the "people" domain, **SDG 3: Good Health and Well-being**, which aims to ensure healthy lives and promote well-being for all at all ages; specifically, target 3.4: "By 2030, reduce by one-third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being."

Within the "people" domain, **SDG 4: Quality Education**, which aims to ensure inclusive and equitable quality education and promote lifelong learning opportunities for all; specifically, target 4.7: "By 2030, ensure that all learners acquire the knowledge and skills needed to promote sustainable development, including, among others, through education for sustainable development and sustainable lifestyles, human rights, gender equality, promotion of a culture of peace and non-violence, global citizenship, and appreciation of cultural diversity and of culture's contribution to sustainable development."

Within the "prosperity" domain, **SDG 9: Industry, Innovation and Infrastructure**, which aims to build resilient infrastructure, promote inclusive and sustainable industrialization, and foster innovation, specifically target 9.5: "Enhance scientific research and upgrade the technological capabilities of industrial sectors in all countries."

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Introduction.

Dementia is a devastating age-related neurodegenerative disorder that affects over 40 million people worldwide (1). The most prevalent cause of dementia is **Alzheimer's disease (AD),** which increases in prevalence with life expectancy and affects 10-30 % of people aged over 65 years (2). The disease was named after Dr. Alois Alzheimer, a German doctor who, in 1906, described the case of a woman who had died of an unusual mental illness characterized by memory loss, language problems, and unpredictable behaviour. Upon autopsy of her brain, he noted abnormal brain tissue (3).

AD is a complex multifactorial disorder, most cases of which lack a clear causative event. This has made the disease difficult to characterize and diagnose. Although some cases are genetically linked, there are many diseases and other factors that can lead to an increased risk of developing AD, including traumatic brain injury, diabetes, hypertension, obesity, and other metabolic syndromes, in addition to aging (4).

Initial symptoms include memory loss, cognitive impairment, and confusion, progressing to full debilitation over time. Ultimately, these symptoms lead to a decline in patients' quality of life and increase the cost of care, which is significant in addressing public health challenges. The disease is characterized by the accumulation of extracellular plaques containing **amyloid beta (Aß)** and **intracellular neurofibrillary tangles (NFTs), inflammation** and **synaptic and neuronal loss.** These are predicted to build up for 10-20 years before the clinical symptoms arise. For this reason, the development of effective treatments is complicated (4,5).

Amyloid precursor protein (APP) is a transmembrane protein which is fragmented by proteases α, ß and γ-secretase. As observed in Figure 1 and 2, Aß is derived from APP via ß-secretase and γ-secretase enzymes successively and aggregates in brain tissue. In AD, inefficient clearance of Aß is the major pathogenic pathway due to the insufficient microglial phagocytic capacity and the increased cytokine levels and downregulated Aß phagocytosis receptors. Instead, NFTs arise from hyperphosphorylation of tau protein (5,6).

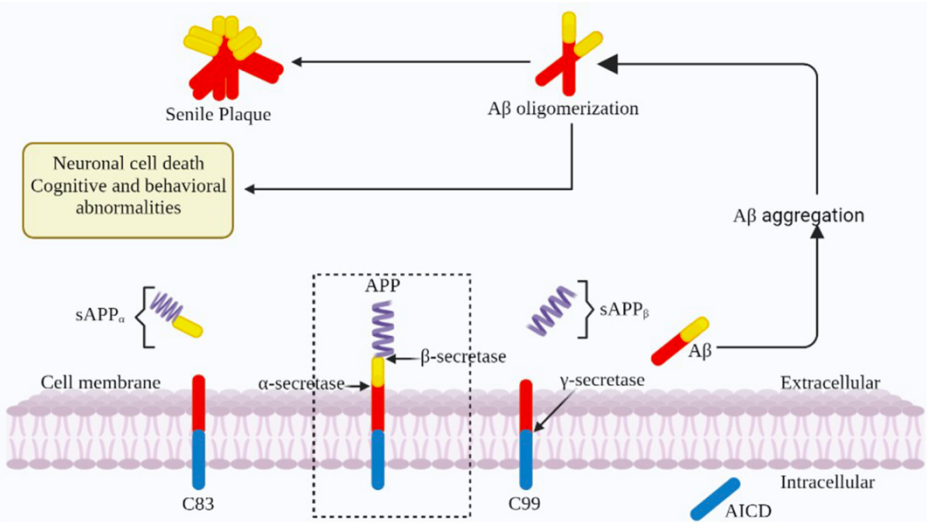

Figure 1: APP's posttranslational modification via ß-secretase and γ-secretase causes the formation of Aß aggregates (7).

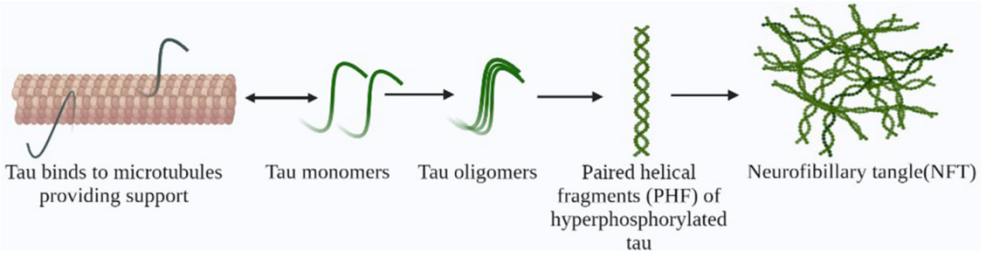

Figure 2: NFTs build-up as a result of hyperphosphorylation of tau protein (7).

In addition, other pathological changes such as inflammation and sustained activation of microglia and other immune cells are also associated with AD. Recently, increasing evidence suggests that inflammation plays a significant role in AD pathogenesis (5). Specifically, there is a large amount of evidence demonstrating the involvement of neuroinflammation in AD pathogenesis (8).

As Alzheimer's disease affects the brain in various ways, it's crucial to understand how the periphery communicates with it. To comprehend the different pathways, one must first consider that the brain is protected from invading substances by tight barriers, including the blood-brain barrier (BBB), the blood-cerebrospinal fluid (CSF) barrier, and the arachnoid barrier. These barriers ensure a balanced and well-controlled microenvironment in the central nervous system (CNS) while providing protection against toxins, infectious agents, and peripheral pro-inflammatory cytokines (9).

Systemically generated inflammatory mediators signal to the brain via alternative pathways, namely via neural and humoral pathways (10). In the neural pathways, peripheral signals (such as cytokines or prostaglandins) activate the **afferent vagal nerve** via receptors located at the vagus nerve fiber terminals. Subsequently, the signal reaches the hypothalamus which leads to physiological responses such as fever. Afterwards, the **efferent vagal nerves** secrete acetylcholine which acts on $\alpha 7$ nicotinic receptors expressed on macrophages, leading to a downregulation of inflammatory cytokines such as TNF (9,11).

Instead, in the humoral pathways, the **circumventricular organs (CVOs)** signal to the CNS across the brain barriers or via activating vascular cells at the brain barriers. The CVOs are stimulated by humoral signals (such as microbial metabolites, cytokines and immune cells that circulate in the blood) and can potentially influence the inflammatory reactions within the brain by modulating microglial activation, affecting myelination, and neurogenesis (12,13).

Additionally, inflammatory molecules and immune cells can also reach the CNS by crossing one of the brain barriers via an active transport system or via a disrupted barrier (such as the blood-CSF barrier). It is important to consider that during **systemic inflammation** brain barrier dysfunction may occur and may allow infiltration of peripheral molecules and immune cells into the CNS, leading to **neuroinflammation** (14,15).

Another possible humoral route involves **systemic perivascular macrophages** (PVMs) or **inflammatory mediators** directly activating signalling pathways in vascular cells, leading to the release of prostaglandins implicated in the development of sickness symptoms such as fever (16).

These pathways are not mutually exclusive; therefore, the effect of systemic inflammation on the brain may result from a combination of the different routes (17). Accordingly, the routes discussed earlier are schematically shown in Figure 3.

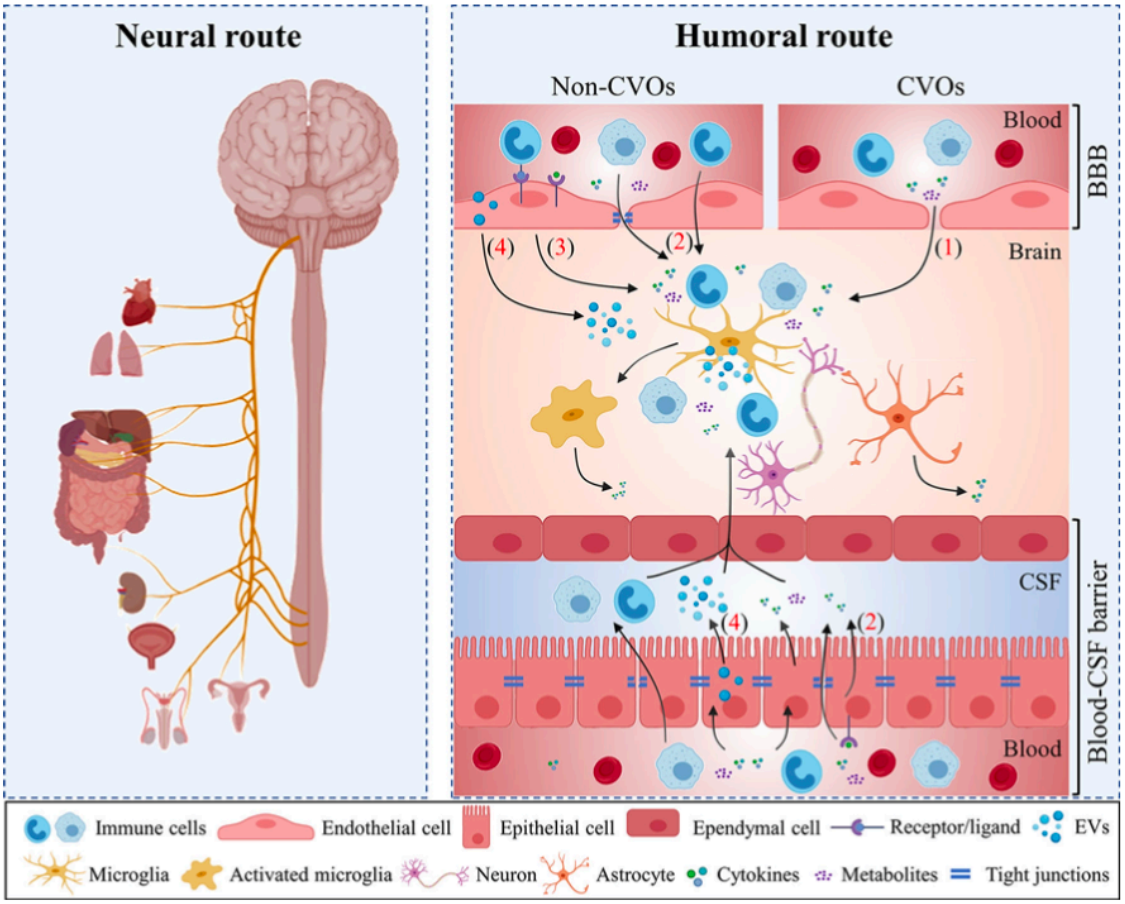

Figure 3: Periphery-to-brain communication pathways. (1) Immune signals enter the brain via special regions called circumventricular organs (CVOs), (2) Molecules from the body's immune system cross into the brain through specific pathways in blood vessels and the choroid plexus, (3) Body-brain communication can activate brain immune cells, leading to microglial activation and neuroinflammation, (4) Immune signals can prompt the release of small structures called extracellular vesicles from brain cells, triggering inflammation. (17)

An early diagnosis is crucial to initiate pharmacological and non-pharmacological treatments, which can help improve quality of life, manage complications, and delay the long-term effects of the disease. Unfortunately, diagnosing AD is challenging as biomarkers are still under research. Thus, the diagnosis of AD still relies on assessing the patient's cognition and function. Guidelines mainly distinguish three stages: the preclinical stage, mild cognitive impairment (MCI), and Alzheimer's dementia (3).

As the global population ages, the importance of finding effective pharmaceuticals for Alzheimer's disease becomes increasingly evident. Furthermore, considering the growing body of evidence linking chronic inflammation to the progression of Alzheimer's disease, studying the mechanisms underlying this relationship holds promise for the development of novel therapeutic interventions in the future.

Objectives.

The main objective of this research project is based on deepening the understanding of the connection between inflammation and the brain, specifically focusing on the potential role of neuroinflammation in the development of Alzheimer's disease. From this perspective, the project aims to address:

- What is chronic inflammation, how it is established and its implications.
- Which are the mechanisms through which Alzheimer's disease is related to chronic inflammation.
- How can we prevent or modulate chronic inflammation through dietary patterns and supplementation to impact the progression of Alzheimer's disease.
- Determine the current existent pharmacological treatments for Alzheimer's disease.

Materials and Methods.

This research project has been carried out following the review method. The search was conducted using databases such as PubMed or Scopus, where access to all the articles was available. Also, online books were consulted through the CRAI resource of Universitat de Barcelona (UB). Additionally, the sources consulted were compared through Scimago Journal & Country Rank (SJR) to verify that the sources were well positioned based on quartiles.

To develop it, a general search was initially conducted to later delve into more specific topics. Information of Alzheimer's disease, the relation with inflammation and different possible therapies and interventions to mitigate this effect. The keywords used included: Alzheimer's disease, inflammation, dietary or nutrition.

The consulted articles were limited to the English language and consideration was given to their recency, primarily from the year 2014 to March 2024.

The bibliography was generated using Zotero, following the Vancouver style.

Results and discussion.

1. Inflammation and chronic inflammation.

Inflammation is a nonspecific defence mechanism of the body in response to tissue damage. There are various conditions that can trigger inflammation, such as pathogens, abrasives, chemical irritants, cellular distortion or alteration, and extreme temperatures. It is a physiological attempt to eliminate toxins, microbes or foreign substances from the injury site to prevent their spread to other tissues and to facilitate tissue repair and restore homeostasis (18). Five symptoms may indicate acute inflammation: redness, heat, swelling, pain and loss of function (19).

In an appropriate response, immune cells are recruited to the affected area via pro-inflammatory signalling pathways, where they initiate activities such as: increasing vascularization, recruiting additional immune cells, and initiating phagocytosis of debris and pathogens. The mediators involved are pro-inflammatory and include transcriptional factors (NF-kß), peptides (bradykinin), cytokines (IL-1ß, IL-6, IL-18, TNF-α, IFN- γ), chemokines (CCL2, CCL3, CXCL8), complement proteins (C1q, C5), enzymes (COX-2, iNOS, LOX), lipids (PGE2) and coagulation factors (platelet activating factor). Eventually, when the trigger of the response is neutralized, immune cells shift their activity towards a pro-resolution phenotype via anti-inflammatory signalling, clearing the debris and repairing the injured tissue (4).

In contrast, **chronic inflammation** is characterized by a prolonged and low-level accumulation of inflammatory substances in tissues and, in some cases, may not be a consequence of acute inflammation but can even be an independent response. Although closely related, acute and chronic inflammation can have seemingly opposing effects on the body (20).

1.1. Inflammation in the brain.

In terms of inflammation, a similar sequence of events occurs in the brain. Regarding neuroinflammation, specific cells and mediators participate in it.

Microglial cells are macrophages that reside in the CNS. **Microglia** account for 10-12% of all cells identified in the brain (7). Under physiological conditions, microglia are neuroprotective; their function is to maintain a healthy brain environment, including the maintenance of synapses, neurogenesis, the regulation of cognitive functions and immunological surveillance (4,8).

Nevertheless, in response to disease, inflammation, or injury, they become activated, leading to the production and release of inflammatory cytokines such as IL-1α, IL-1ß, TNF-α, or RONS, and they are involved in phagocytosis, resulting in a pro-inflammatory response (8). In the resolution phase, the excess microglia are removed by a dual mechanism of cell egress and apoptosis to re-establish the stable microglial network (21).

Microglial activation in Alzheimer's disease is thought to be potentiated by Aß peptides, tau and neuronal degradation (22). In neurodegenerative disorders such as AD, microglia have prominent roles in the activation of the nuclear factor-kappa ß (NF-kß) pathway, known as an

important pro-inflammatory transcriptional factor that has explicit functions in gene expression, immunity modulation of inflammation, and disease progression (23).

Evidence continues to confirm that in the aged and neurodegenerative brain, there is a primed microglial state that elicits an "aggressive phenotype" in response to the inflammatory changes, resulting in a local production of proinflammatory cytokines. However, the levels at which these cytokines have specific inflammatory effects are context-dependent, and depend on interindividual variability (11,24).

Similar to microglia, **astrocytes**, representing the 20-40% of mammalian brains, play multiple roles in organizing and maintaining brain structure and function (4). It has been proposed that activation of the transcriptional factors such as signal transducer and activator of transcription 3 (STAT 3) and NF-kß, is at least related in part related to their protective (25) and detrimental (26) phenotypes, respectively.

Regarding their relationship with AD, Aß triggers an inflammatory response mediated by glial cells, contributing to cognitive decline and degeneration. Aß also causes the production of inflammatory and proinflammatory chemicals from astrocytes that overlap and are comparable to those produced by microglia. In cell models of AD, astrocytes activated by Aß may secrete inflammatory compounds that harm synaptic and neuronal function (7).

Finally, **blood-derived mononuclear cells** (as perivascular macrophages) may also contribute in some manner in clearing CNS Aß deposits (7).

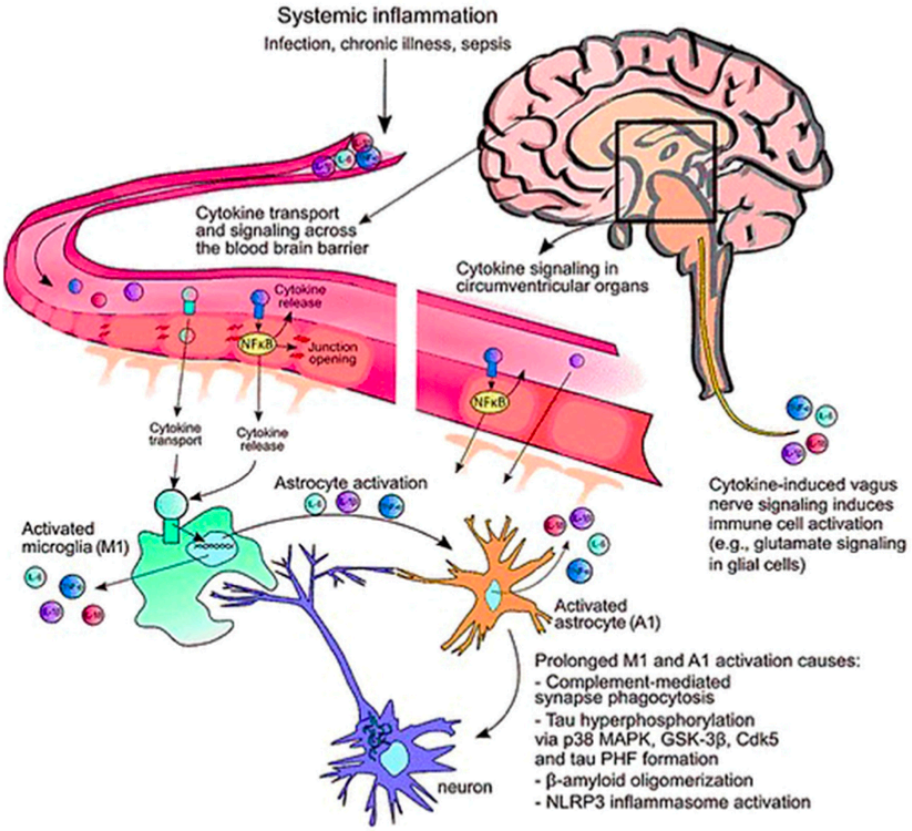

Figure 4. Systemic inflammation, neuroinflammation and Alzheimer's specific pathways (7).

As depicted in Figure 4, systemic inflammation may trigger the activation of microglial cells, subsequently leading to the activation of astrocytes. Prolonged activation of both microglia and astrocytes can result in various effects associated with AD, including complement-mediated synapse phagocytosis, tau hyperphosphorylation through different pathways, formation of tau paired helical filaments (PHF), ß-amyloid oligomerization, and activation of the NLRP3 inflammasome. The NLRP3 is an intracellular protein structure that plays a pivotal role in the body's inflammatory response.

1.2. The effect of aging.

Several environmental risk factors for the development of AD share systemic pro-inflammation as a common characteristic. Aging, the most prevalent risk factor for AD, is accompanied by a low-grade systemic inflammation and a relative decline in adaptive immunity and T helper 2 (Th2) cell response, a concept known as **inflammaging.** This is caused by an imbalance between pro- and anti-inflammatory mediators (9).

Immunosenescense, which occurs as individuals age, also needs to be considered. This gradual deterioration affects both the peripheral and central components of the immune system, increasing susceptibility to infections and disease. Altered expression of several immune-related genes has been observed in some regions of the aged human brain, a pattern which is exacerbated in AD (27).

Aging also causes changes at the cellular level, with **microglia** showing substantial phenotypic changes. The baseline level of inflammation may increase upon repetitive inflammatory stimuli, impairing the ability of microglia to perform basic physiological functions and likely contributing to neurodegenerative processes. In contrast, young microglia can more efficiently phagocytose disease-related proteins, such as Aß (28). However, microglial efficacy in Aß removal diminishes during aging, particularly in AD (28,29). Despite their inability to clear Aß, they continue releasing pro-inflammatory mediators to further stimulate the immune response, creating a vicious cycle that leads to the accumulation of activated immune cells, inflammatory mediators, and Aß (30).

As previously mentioned, the brain is shielded from invading substances by multi-layered meninges: the blood-brain barrier (BBB), the blood-cerebrospinal fluid (CSF) barrier and the arachnoid barrier. Endothelial cells, pericytes, and astrocytes at the BBB are especially vulnerable to the effects of aging and chronic stimulation by inflammatory mediators (4), as depicted in Figure 5.

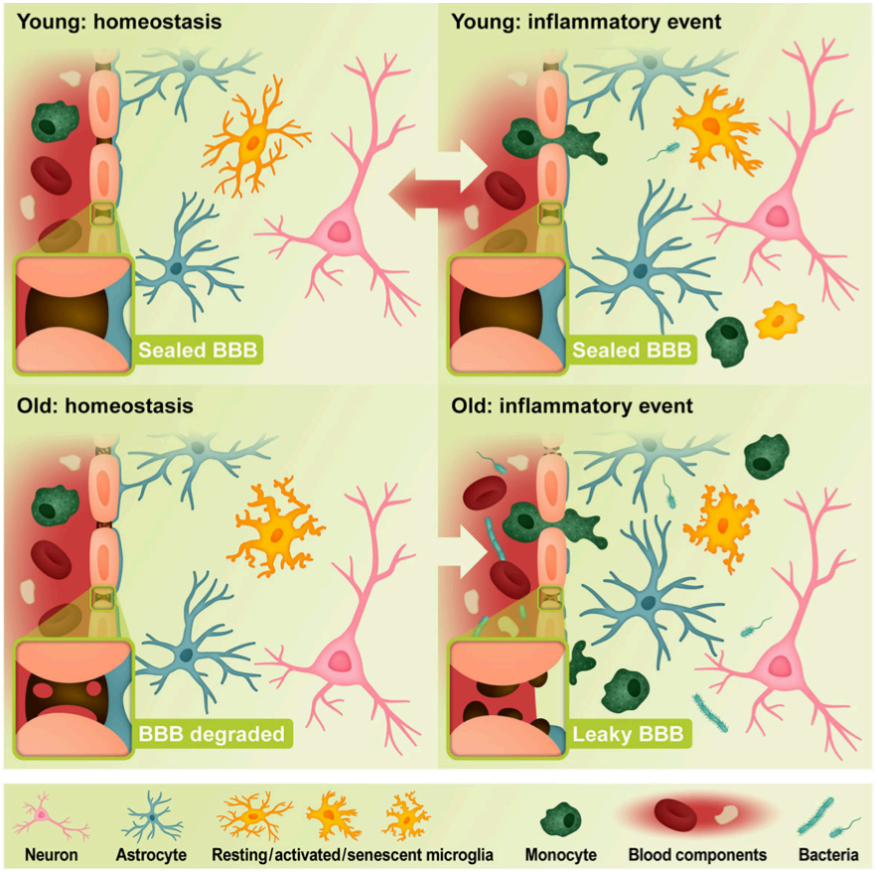

Figure 5. Inflammatory responses in the young and old brain. In the young brain, the BBB is intact, sealed. In the old brain, the BBB is degraded, and its cellular components also suffer from aging effects. The leaky BBB leads increased inflammatory cell migration (4).

Tight junctions (TJs) prevent the accumulation of harmful compounds in the CSF and the brain (31). Therefore, a possible mechanism that could explain the impairment in the BBB function is the immune-related senescence of its cellular components (4).

Inflammatory cytokines, such as TNF, IL-1, IL-17A are one factor contributing to BBB malfunction, being implicated in the ability of the TJs and BBB permeability. Several *in vitro* and *in vivo* studies show that systemic inflammation has disruptive effects on BBB integrity leading to the diffusion of peripheral inflammatory factors into the brain. However, Aß build-up can also cause BBB dysfunction through endothelial toxicity and enhanced monocyte adhesion. (7,32). Although the loss of BBB integrity seems to occur before hippocampal atrophy and cognitive impairment, suggesting that this precedes the neurodegenerative process in AD (33,34).

All these factors induce changes in the brain that are associated with an increased cognitive decline in AD patients (9).

2. Inflammation in Alzheimer's disease:

Inflammatory mediators have been consistently observed in the AD brain over the years. Typically, these mediators are found at undetectable levels in samples from nondemented elderly patients, and have been studied through immunohistochemical, biochemical, and molecular approaches. Many of these findings were initially disregarded due to the belief that the brain was immune privileged. However, it is now evident that while the brain may possess numerous unique immunological properties, it is not completely isolated from immunological processes (35).

2.1. The production of Aß and how chronic inflammation induces tau phosphorylation and exacerbates pathology.

Aβ accumulation is widely known as one of the main triggers of the neurodegeneration associated with Alzheimer's disease. However, evidence suggests that Aß may act as a physiological trigger of pro-inflammatory responses during healthy aging. Meaning that its build-up would be related with aging and immunosenescense effects, causing a dysregulation of the Aß peptide (4).

The key remains in the different functions that Aß performs in the body depending on its quantity. At picomolar to nanomolar concentrations, modulates synaptogenesis, axonal growth and guidance, synaptic plasticity, oxidative stress, learning, and memory. At higher concentrations, as part of the physiological acute innate immunity, it binds to inflammatory receptors, activates immune-related transcriptional factors as NF-kß, produces inflammatory mediators, and exerts potent antimicrobial activity (4).

Besides, it has been demonstrated that **inflammatory mediators** (TNF-α, IFN- γ and IL-1ß) induce the expression of ß-secretase-1 (BACE1) and release of Aß in astrocytes, suggesting its contribution to the amyloidosis in AD (36). These studies suggest that chronic inflammation is a potential contributor to the overproduction of Aß in AD. Still, more investigation is required to know if the increase of inflammation can trigger the excessive production of Aß on its own (4). In terms of Aß levels, **immune-related clearance mechanisms** need to be considered. For example, clearance through phagocytosis and intracellular degradation, and transcytosis across the BBB mainly by a transmembrane protein such as LRP-1. It is an important receptor for the uptake of Aß by astrocytes, neurons, and endothelial cells. (37–39). Human studies in aged AD subjects indicate that brain LRP-1 expression decreases and inversely correlates with the age of onset of AD (40). This decline in LRP-1 levels may be another factor contributing to the increase in inflammation and Aß accumulation in the brain during aging process (4).

Based on the evidence linking inflammation to the accumulation of Aß in AD, many potential therapeutic approaches involving mediators implicated in the activation and resolution phases of inflammation may be considered. However, the integration between inflammation and AD is not straightforward (4).

Studies have shown controversial results which illustrate the complexity of targeting distinct inflammatory mediators in AD. On the one hand, both anti-inflammatory and pro-resolution mediators have produced mixed results. For instance, the activation of IL-10 (anti-inflammatory

signalling) in AD mouse models resulting in deficient Aß phagocytosis and exacerbated AD neuropathology (41,42). On the other hand, stimulation of anti-inflammatory LXA_4 or prostaglandin EP4 receptor signalling facilitated microglia Aß clearance and reduced AD-like pathology in mice (43,44).

Taken altogether, studies demonstrate the **importance of the phagocytic activity of microglia in the clearance of Aß deposits.** Therefore, the development of strategies that could stimulate the protective phagocytic phenotype while inhibiting the detrimental pro-inflammatory phenotype may present a challenging therapeutic approach (4).

Moreover, the role of chronic inflammation in inducing **tau phosphorylation** in AD becomes apparent when considering the direct interaction between neurons and microglia, as well as the subsequent activation of neuronal protein kinases and phosphatases by inflammatory signals. Neurons express inflammatory receptors and molecules, including complement that allow them to interact directly with microglia (45). As mentioned before, microglia become activated in response to inflammation. Therefore, inflammatory signals can consequently activate neuronal protein kinases and phosphatases such as cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase-3ß (GSK3ß), extracellular regulated kinases (ERK) and protein phosphatase 2A (PP2A), which regulate tau phosphorylation (46–48).

It appears evident that chronic microglial activation and inflammation cause the propagation of pathological tau species and participate in tau-induced neurotoxicity (49). Furthermore, most studies have shown that chronic levels of inflammatory mediators exacerbate the activation of key protein kinases that control the phosphorylation levels at tau (4).

2.2. The differing effects of inflammation on Aß and tau pathology.

On the one hand, it has been shown that activation of IL-1ß signalling (an effect that also occurs due to aging) leads to the activation of kinases (CDK5, GSK3ß) and p38 mitogen-activated protein kinase (p38-MAPK), resulting in tau hyperphosphorylation and cognitive impairment in the 3xTg-AD mouse model (50). On the other hand, opposed effects were shown for Aß in the overexpression of IL-1ß in the same mouse model, reducing the overall levels of Aß plaques by increasing the number of activated microglia surrounding Aß plaques (51).

For all these reasons and considering that tau levels better correlate with the cognitive decline during the disease process, significant concerns are raised regarding the clinical efficacy of therapies designed to inhibit or activate inflammation in AD (52).

2.3. Role of intracellular signalling pathways.

Intracellular signalling pathways play pivotal roles in regulating various cellular processes, orchestrating responses to external stimuli, and maintaining cellular homeostasis. These pathways serve as networks of molecular communication within cells, transmitting signals from the cell membrane to the nucleus to modulate gene expression and cellular functions. Understanding the intricacies of these signalling cascades is essential for unravelling their

contributions to physiological and pathological processes, including neuroinflammation and neurodegenerative disorders like AD (53).

Mitogen-activated protein kinase (MAPK)

This group of signalling pathways is one of the most common ways to control eukaryotic cells. It comprises six different families, including p38 (α/ß/γ/δ), ERK1/2 (extracellular regulated kinases), JNK 1/2/3 (JUN NH2 terminal kinases), ERK 7/8, ERK 3/4 and ERK5 (54).

The impact of lipopolysaccharide (LPS), cytokines, or Aß-induced neuroinflammation underscores the significance of MAPK signalling pathways. This suggests that it might be possible to hinder neuroinflammation through the modulation of MAPK signalling pathways (7).

Nuclear Factor Kappa ß (NF-kß)

The importance of this pathway is particularly highlighted in relation to neurological disorders and nervous system development. NF-kß signalling is activated through both the noncanonical and canonical routes. Specifically, the canonical route is well-researched and plays a crucial role in inflammatory reactions, which are a fundamental aspect of AD progression. Therefore, the persistent inflammation observed in AD is triggered by the activation of NF-kß signalling and the subsequent release of cytokines and chemokines from microglia (7).

Peroxisome proliferator-activated receptors (PPAR-γ)

PPAR-γ has been demonstrated to affect a wide range of genes associated with various functions. It is suggested that PPAR-γ could play an essential role in regulating pathophysiological aspects of AD. For instance, PPAR-γ agonists have shown promise in this regard. However, research also indicates that PPAR-α and PPAR-δ may play crucial roles in the pathogenesis of neuroinflammation (7,55).

2.4. Genetic risk factors for AD that are involved in inflammatory responses.

Numerous single nucleotide polymorphisms (SNPs) have been associated with an increased risk of Alzheimer's disease (AD). Some examples of these genes include **TREM2, ApoE4, CD33, CR1, ABCA7,** and **SHIP1**, which give rise to these SNPs and encode proteins that are crucial for microglial function and inflammation (56).

The Apolipoprotein E (ApoE) isoforms have important relevance to inflammation. It is the most prevalent genetic risk factor for late-onset AD. As a polymorphic lipoprotein, it mediates the transport and delivery of cholesterol and other lipids through cell surface ApoE receptors. The ApoE4 isoform confers the highest risk for AD (4).

ApoE also has many roles in the CNS, such as lipid homeostasis, repair of injured neurons, maintenance of synaptic-dendritic connections, and scavenging toxins including Aß. It is also an important modulator of immune responses and has an anti-inflammatory effect (4).

Diverging from the other isoforms, the mere expression of ApoE4 can potentiate immune activation with aging, eventually leading to neurodegenerative disease. This may occur due to its potential loss of anti-inflammatory properties and inefficient prevention of the detrimental impact of inflammation (4).

ApoE is also an endogenous ligand for TREM2. Therefore, their interaction appears necessary to mediate the switch from a homeostatic to a neurodegenerative microglial phenotype. The extracellular soluble TREM2 (sTREM) activates microglia via the Akt-GSK3ß pathway, leading to the activation of the NF-kß transcription factor and consequently to the transcription of pro-inflammatory cytokines. Notably, the level of sTREM is elevated in the cerebrospinal fluid and plasma in AD, correlating with overall patient inflammation. Despite the importance of TREM2 expression in microglia for the removal of pathological tau species, an overactivation of these cells and the resultant chronic inflammation have a detrimental effect on tau function (4).

Ultimately, evidence indicates that the receptors TREM2 and CD33 might serve as a regulatory mechanism for microglial phagocytosis in healthy individuals. However, this mechanism is disrupted in AD, where gene expression shifts towards increased microglial reactivity and pro-inflammatory responses (4).

2.5. Gut inflammation.

Bacteria, fungi, archaea, virus and protozoa collectively form our gut microbiota, acting in a symbiotic manner beneficial to the host. Despite the anatomical separation between the CNS and the gastrointestinal system, there exists a bidirectional network called "**gut-brain axis**". Due to evidence of the gut microbiota's role in maintaining the normal physiology and health of the host, interest in its role in AD has increased. An altered gut microbiota may play an important role in AD through an underlying intestinal inflammatory process. The interaction can occur *via* two routes: *via* vagal transmission and *via* systemic circulation (17,57)

Gut bacteria activate the **vagus nerve** directly or indirectly through their metabolites and neuroactive substances that interact with thousands of sensor and motor fibres from the vagus nerve that connect with the brainstem (17).

The vagus nerve is a physical conduit between gut microbial activity and neuroinflammation. Effective vagal nerve signalling is critical for sending appropriate signals to microglia in order to modulate levels of neuroinflammation (58).

Changes in the composition of the gut microbiota, referred as **dysbiosis**, have been associated with aging and the development of inflammatory and CNS disorders including AD (59).

It is known that **intestinal inflammation** induced by perturbations in the gut microbiota is directly associated with dysfunction of the intestinal barrier. This dysfunction allows the entry of pathogenic, immune-stimulating and neuroactive substances into the systemic circulation, possibly contributing to increased microglial activation and production of pro-inflammatory cytokines in the brain (60). This suggests that the gut microbiota dysbiosis observed in the elderly could contribute to peripheral inflammation, therefore exacerbating neuroinflammation and AD (4).

Gut microbiota-derived metabolites also need to be considered as additional contributors to the gut-brain crosstalk. Microbial metabolites, such as neurotransmitters, short-chain fatty acids

(SCFAs), and trimethylamines, can potentially influence microglial activation direct or indirectly (57,61).

A study comparing the gut microbiota of individuals with and without AD revealed that AD participants had decreased microbial richness and diversity, with low abundance of *Firmicutes* and *Bifidobacterium*, and a notable increase in the abundance of *Bacteroidetes*. Additionally, this variation in microbial diversity correlated with cerebrospinal fluid biomarkers of AD pathology (62).

2.6. Chronic diseases.

Chronic diseases like obesity, diabetes, atherosclerosis, and depression are also suggested as potential risk factors for developing AD due to their association with chronic inflammation. It is known that chronic diseases have an abnormal inherent metabolism that indices a general pro-inflammatory response in peripheral organs. This sustained chronic inflammatory situation can, among other effects, disturb the interfaces between the blood and the brain, enabling substances from the periphery to enter the brain. This, might induce persistent chronic brain inflammation resulting in problems with brain function, including cognitive impairment in AD (12,17).

Due to the association between aging and these metabolic disorders, it is difficult to study the contribution of aging to AD in isolation from other age-dependent disorders. Although primarily associated with metabolism, obesity, hypertension, and type 2 diabetes mellitus (T2DM), have also been shown to lead to increased peripheral inflammation. Therefore, excessive inflammatory mediators produced for example, by adipose tissue during metabolic syndrome, affect the brain, stimulating microglia and causing synaptic pruning, and perhaps initiating the accumulation of Aß (4).

While further mechanistic studies are needed to directly connect the alterations in the immune system resulting from metabolic disorders and AD, these discoveries reinforce the complexity between inflammation and genetic and lifestyle factors. These factors may collectively heighten the risk of developing AD (4).

3. Prevention and treatment of Alzheimer's disease.

As the global prevalence of Alzheimer's disease continues to rise, prevention strategies have become increasingly crucial. Research suggests that lifestyle factors, including diet, play a significant role in the development and progression of the disease. Adopting a healthy diet, such as the Mediterranean diet (MedDiet) or Mediterranean-DASH intervention for Neurodegenerative Delay diet (MIND), has been associated with a lower risk of cognitive decline and AD. In addition to dietary patterns, supplementation with specific nutrients has been investigated for their potential role in AD prevention.

By incorporating these dietary patterns and supplements into daily routines, individuals may be able to reduce their risk of developing AD and promote overall brain health. However, further research is needed to better understand the mechanisms underlying the protective effects of

diet and supplementation and to optimize preventive strategies for AD. Aditionally, pharmacological treatments are available to manage the symptoms and slow the progression of the disease. In the realm of AD, ongoing advancements in pharmacological treatments expected to offer significant breakthroughs.

3.1. Prevention of Alzheimer's Disease with dietary patterns.

Mediterranean diet (MedDiet).

Although several food combinations and patterns exist, the dietary habits of people living around the Mediterranean basin consist primarily of plant-based foods: fruits, vegetables, minimally processed cereals, legumes, nuts, and olive oil as the primary source of fat. It also includes moderate amounts of dairy products (mainly fermented such as cheese and yogurt), low to moderate amounts of fish and poultry, red meat in low amounts, and wine, consumed modestly, normally with meals (63).

The "Mediterranean lifestyle" is also a widely spread concept. This term encompasses typical eating habits, lifestyle choices, and cultural elements, such as moderation and simplicity in food consumption, a preference for seasonal, fresh, and minimally processed foods, the promotion of traditional, local, environmentally friendly, and diverse products, and social interaction, while allocating sufficient time and space to culinary activities. The lifestyle includes the regular practice of moderate physical activity (at least 30 minutes per day), along with adequate sleep and daytime rest (naps), as essential complements to the dietary pattern (63).

Dinu et al. summarized the evidence in an umbrella review of meta-analysis of observational studies and randomized clinical trials (RCTs) for a total population of over 12,800,000 subjects. Robust evidence, supported by a P-value < 0.001, a large simple size, and not a considerable heterogeneity between studies, for a greater adherence to the Mediterranean diet and a reduced the risk of neurodegenerative diseases (including AD), as well as overall mortality, cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, and diabetes, was found (64).

Among healthy dietary patterns, the MedDiet has demonstrated the highest quality evidence supporting its positive impact on cognition. It is true that the associations between nutrition and cognition are complex because of the multidimensional nature of nutrition, multiple neurological pathways influencing cognition, diverse cognitive domains, and the complexity of cognition itself (65).

Overall, the existing evidence to date regarding the MedDiet and cognitive decline strongly suggests protective effects. There are numerous neurobiological mechanisms that could be responsible for the potentially protective links between the MedDiet and cognitive function, including vascular function, oxidative stress, inflammation, amyloid aggregation, neurodegeneration, synaptic function, and brain structural connectivity (65).

Furthermore, two longitudinal studies involving repeated amyloid imaging PET scans have indicated that higher adherence to the MedDiet is associated with lower rates of cerebral

amyloid accumulation. This suggests a potential link between this dietary pattern and the brain amyloidosis observed in AD (66,67).

To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet, a study was conducted at the **PREDIMED cohort** (PREDIMED-Barcelona). A total of 447 cognitively healthy volunteers (52.1% women, mean age 66.9 years) were assessed at baseline and after 4.1-years of follow-up. Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin oil (1L/week) or with mixed nuts (30 g/day) or a control diet with advice to reduce dietary fat. Cognitive change over time was assessed using a battery of six neuropsychological tests. The study concluded that a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function. Importantly, these benefits were independent of sex, age, energy intake, and various cognition-related variables, including education level, APOE ε4 genotype, and vascular risk factors (65,68).

Mediterranean-DASH intervention for Neurodegenerative Delay diet (MIND).
The MIND diet, which combines the Dietary Approaches to Stop Hypertension (DASH) and the MedDiet, was developed to improve brain health and delay cognitive decline. It emphasizes the consumption of berries and green leafy vegetables, but does not specify high fruit and fish intake (69).

A systematic review was conducted to assess the relationship between Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) diet and cognitive functioning in older adults. Thirteen articles were included in the review (nine cohort, three cross-sectional, and one RCT studies), indicating that adherence to the MIND diet was positively associated with specific, but not all, domains of cognition and global cognitive function (78% of the studies) in older adults. The conclusion was that the MIND diet was superior to other plant-rich diets, such as MedDiet, DASH, Pro-Vegetarian and Baltic Sea diets, for improving cognition (70).

However, a review found that all three diets (Mediterranean Diet, DASH, and MIND) were linked to reduced cognitive decline and a decreased risk of Alzheimer's disease, highlighting the significance of olive oil as a key component. It needs to be considered that the strongest associations were observed for the MIND diet (71).

3.2. Dietary supplements in Alzheimer's Disease.

The following table summarizes the information gathered from various studies aimed at assessing the effect of different types of supplementations (probiotic-fermented milk, omega-3 fatty acid, alpha lipoic acid, phosphatidylserine and phosphatidic acid, betaine, soy isoflavones, Souvenaid®, and a nutraceutical formulation) in patients diagnosed with Alzheimer's disease, in order to evaluate the progression of the disease's effects.

Table 1. Studies evaluating the effect of different types of supplementations in patients diagnosed with Alzheimer's disease.

Ref	Objective	Methods	Markers	Results	Conclusion
(72)	Prove that continuous dietary supplementation with milk fermented with kefir grains might improve cognitive and metabolic and/or cellular disorders in AD patients. Based on the notion that several studies have demonstrated inflammation and oxidative stress preceding the cardinal neuropathological manifestations of AD.	Uncontrolled clinical trial. 2 ml/kg/day **probiotic-fermented milk** supplementation for 90 days. N=13, AD patients exhibiting cognitive deficit (clinical diagnostic with increased level of certainty defined by the Alzheimer's association and the National institute on Aging (NIA). Women (n=11) - 78.7 ± 3 years - 1.85 ± 0.7 treatment duration (years) Men (n=2) - 78 ± 7 years - 0.6 ± 0.1 treatment duration (years)	Cognitive assessment Cytokine expression Systemic oxidative stress levels Blood cell damage biomarkers	Kefir supplementation showed beneficial effects in AD patients. Cognitive dysfunction (↑ memory, visual-spatial and abstraction, executive and language functions) Systemic inflammation (↓ IL-8, IL-12, TNF-α, IL-8/IL-10, IL-12/IL-10) Oxidative stress (↓ ROS, AOPP, ↑ NO) Mitochondrial damage (↓ mitochondrial potential) DNA damage and repair (↓ DNA fragmentation, ↑ cell cycle arrest, ↑ p53, ↓ PARP-1 cleaved) ↓ Apoptosis	Symbiotic supplementation for 90 days had reparatory favourable effects on cognitive dysfunction, systemic inflammation by reducing proinflammatory cytokines, systemic oxidative stress and blood cell damage (analysed by DNA damage/repairment and apoptosis).

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(73)	The study was designed to evaluate the effects of supplementation with omega-3 fatty acids alone or plus alpha lipoic acid compared to placebo on oxidative stress biomarkers in AD. Because several epidemiologic studies have reported a decreased risk of AD with fish consumption.	Randomized placebo-controlled pilot trial of **omega-3 fatty acids** and **alpha lipoic**. 12 months. N=39 n=13 placebo → n=11 completed n=13 (Omega-3) → n=11 completed n=13 (Omega-3+LA) → n=12 completed Omega-3 only group = fish oil concentrate in the triglyceride form at 3 g/day (675 mg DHA, 975 mg EPA) Omega-3 + LA = same omega-3 only group supplementation + 600 mg/day of LA in the racemic form.	Omega-3 levels, LA levels Urine F2-isoprostane levels Cognitive measures (ADAS-cog, MMSE) Functional measures (ADL/IADL)	Compared to placebo, there was no significant difference at 6 or 12 months in the primary outcome measure, urinary F2 isoprostane levels. There appeared to be no treatment effect on biomarkers of lipid or protein oxidation. The study did not demonstrate a treatment effect on ADAS-cog change over 12 months. However, both treatment arms showed a delay in progression of functional impairment (IADL) when compared to placebo over 12 months. The omega-3+LA group showed a slowing global cognitive decline as measured by MMSE that was not seen in the placebo or omega-3 groups.	The combination of omega-3 + LA slowed both cognitive and functional decline in mild to moderately impaired AD participants over 12 months.

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(74)	A decline of phospholipids, particularly phosphatidylserine (PS) in neuronal membranes has been associated with memory impairment and deficits in mental cognitive abilities. As PS and phosphatidic acid (PA) are found in the neuronal membrane, this has led to the proposal that their administration may prevent or reverse age-related neurochemical deficits.	Double-blind, randomized, placebo-controlled trial of 300mg **phosphatidylserine (PS)** + 240mg **phosphatidic acid (PA)** /day. 2 months. Patients with AD n=96 n=53 (*2 drop-outs) PA+PS n=39 placebo 61 women and 35 men	Wechsler Memory Scale (WMS) Mood changes (LDS) Self-reported general condition Post-trial consumption	In the PS+PA there was a highly significant increase in the global WMS score and also in the test's components: information, visual memory and memorizing numbers. The placebo group experienced a significant increase in depressive symptoms, whereas the PS+PA group revealed no significant change. The PS+PA reported an improvement in their general condition compared to the placebo group. The indicator of post-trial consumption rates revealed a large difference between the groups. Patients in the PS+PA group decided to continue the supplementation at their own expense (P = 0.010).	Short-term supplementation with PS+PA in patients with AD showed a stabilizing effect on daily functioning, emotional state and self-reported general condition.

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(75)	AD is associated with malnutrition and hyperhomocysteine. Betaine is a methyl donor for Hcy remethylation. The current study aimed to analyse the relationship between malnutrition and hyperhomocysteine in AD patients, and effects of diet intervention with betaine on the disease.	Randomized placebo-controlled trial. All patients were randomly assigned into an untreated group and intervention group (50, 100 and 200 ug/kg **betaine** for 1 month). N=97 patients with AD. Mean age = 74.6 ± 9.2 According to MNA-SF n=36, non-malnutrition group n=61, malnutrition group 65 healthy subjects in the control group.	By enzymatic cycling assay, Western blot and ELISA: Levels of high homocysteine. Tau hyper-phosphorylation Synaptic proteins. Blood inflammatory factors. The cognitive function was measured by ADAS-cog.	There was a significant difference in mental status between normal people and AD patients (P<0.5). Betaine decreased the levels of phosphorylated tau, elevated PP2Ac activity and inhibited Aß accumulation (P<0.5). IL-1ß and TNF-α were significantly higher in the untreated group while much lower in the intervention group (P<0.5). Betaine can effectively suppress inflammation and trigger an increase in memory-related proteins. Also, the expression level of Hcy can be restored. ADAS-Cog suggested that significant improvement was found after the intervention with betaine.	AD was associated with both malnutrition and higher levels of Hcy. Betaine could restore Hcy expression to normal level in AD patients, which might ameliorate memory deficits.

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(76)	Based on the hypothesis that older adults with AD treated with soy isoflavones would exhibit domain-specific cognitive changes, such as improvements in visual spatial abilities, language fluency, and speeded dexterity, rather than global cognitive effects. The trial aimed to examine the potential cognitive benefits of soy isoflavones in patients with AD.	Double-blind, randomized, parallel-group design study. 100 mg/day **soy isoflavones** (85 % **daidzin** and **genistin**) or matching placebo capsules for 6 months. N=65 (34 women, 31 men). 59 subjects completed all study visits. APOE4 genotype was determined for all participants.	Cognitive outcomes. Plasma isoflavone levels. (measured at baseline and at three and six months after baseline)	Plasma levels of isoflavones rose in individuals who received soy isoflavone treatment compared to their initial levels and to those who received a placebo. However, there was considerable variation in plasma levels among individuals. No significant differences in treatment effects for cognition emerged between treatment groups or genders. Exploratory analyses of the relationship between changes in cognition and plasma isoflavone levels showed a link between equol levels and improved speed in dexterity and verbal fluency.	This six-month treatment of 100 mg/day with soy isoflavones did not show cognitive benefits in older individuals, both men and women, who had Alzheimer's disease.

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(77)	The trial aimed to investigate the effect of a medical food (Souvenaid®, a multinutrient drink designed to improve synapse formation) on cognitive function in people with mild AD.	Randomized, double-blind controlled trial. **Souvenaid®** or a control drink taken once-daily for 12 weeks. N=225 (diagnosis of probable AD) n=113 allocated to active product → 99 included in 12-week efficacy analysis → 86 entered extension phase → 84 included in 24-week efficacy analysis n=112 allocated to control product → 100 included in 12-week efficacy analysis → 83 entered extension phase → 77 included in 24-week efficacy analysis	Delayed verbal recall task of the Wechsler Memory Scale-revised, and the 13-item modified AD Assessment Scale-cognitive subscale at week 12	At 12 weeks, significant improvement in the delayed verbal recall task was noted in the active group compared with the control group (P=0.021). Modified AD Assessment Scale-cognitive and other outcome scores were unchanged. The control group neither deteriorated nor improved.	Supplementing with a medical food containing phosphatide precursors and cofactors (Souvenaid®) for 12 weeks resulted in enhanced memory, specifically in delayed verbal recall, among patients with mild AD.

Table 1. (continued)

Ref.	Objective	Methods	Markers	Results	Conclusion
(78)	Determine whether nutritional intervention could positively impact cognitive performance and behavioural difficulties for individuals diagnosed with AD.	Double-blind, randomized, multi-site, phase-II study. N=106 individuals with AD were randomized to a nutraceutical formulation **(NF: folate, alpha-tocopherol, B12, S-adenosyl methionine, N-acetyl-L-carnitine)** or placebo for 3 or 6 months. Then, participants received NF for 6 additional months (open-label extension).	Clox-1 (executive clock drawing task) Dementia rating scale Neuropsychiatric inventory Activities of Daily Living	The NF cohort improved versus the placebo cohort within 3 months (Clox-1 p=0.0083, Dementia rating scale p=0.0266). However, caregivers reported non-significant improvements in neuropsychiatric inventory. Activities of Daily Living did not change for either cohort. Both cohorts improved or maintained baseline performance during open-label extensions.	These findings extend phase I studies where NF maintained or improved cognitive performance and mood/behaviour.

In the open-label extension: The main focus was on assessing cognitive performance, with additional attention given to behavioural and psychological symptoms of dementia (BPSD) and activities of daily living. Participants were able to sustain their cognitive performance and BPSD at their initial levels throughout the 12-month period. These results align with previous placebo-controlled studies showing improvements in cognitive performance and BPSD with NF, in contrast to the usual decline observed in participants receiving a placebo (79).

3.3. Physical activity (PA) and exercise interventions on AD.

Exercise is widely recognized as essential for overall health and well-being, with emerging evidence suggesting its potential as a cost-effective and low-risk co-adjuvant therapy in delaying cognitive decline and functional impairment in AD patients. Numerous studies have highlighted the benefits of exercise, prompting further investigation into its mechanisms and effects on AD progression (80).

An umbrella review of existing meta-analyses delved into the association between physical activity (PA)/exercise and AD risk, as well as the impact of exercise interventions on disease progression. Strong meta-analytical evidence indicates that regular PA reduces the risk of incident AD, while also improving cognitive function, physical performance, and functional independence in AD patients. However, further research is needed to determine the optimal exercise parameters for maximal benefits (81).

Exercise induces a cascade of cellular and molecular processes in the brain, promoting angiogenesis, neurogenesis, synaptogenesis, and the release of neurotrophic factors that enhance learning, memory, and brain plasticity. Notably, exercise has been found to modulate Aß turnover, inflammation, and cerebral blood flow, thus exerting positive effects on AD pathology (82). Moreover, the benefits of exercise extend beyond genetic predispositions, such as the APOE ε4 allele, the strongest genetic risk factor for late-onset AD. Engaging in regular exercise has been shown to mitigate AD risk regardless of genetic background, although the underlying mechanisms may vary (83).

Reviews have consistently highlighted the role of physical activity in maintaining cognitive function, modifying the risk of cognitive decline, AD, and dementia. Despite strong evidence supporting the contribution of physical activity to healthy brain aging, further research is needed to elucidate the underlying mechanisms, particularly in human populations (84).

3.4. Current pharmacological treatments and new therapeutic approaches.

At present, there is no cure for Alzheimer's disease, and there is no treatment that can stop the underlying disease from progressing. However, several drugs are approved to help stabilize the disease or postponing symptom deterioration for a period ranging from several months to a few years. These medications work by regulating neurotransmitters in the brain, although their efficacy leaves a lot to be desired. While the ultimate aim remains finding a cure for AD and reversing its detrimental effects, any successful strategy to slow down or prevent the advancement of the disease would have a significant socio-economic impact worldwide, given the current epidemiological situation. (4,7)

Currently, two classes of drugs are used: cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and N-methyl-D-aspartate receptor (NMDAR) antagonists (memantine). Because they work in different ways, cholinesterase inhibitors can be safely used along with NMDA antagonists. The following table (Table 2) lists the key medications used for AD, whereas Figure 6 highlights the pharmacological management.

Table 2: Authorized and used medications in daily clinical practice for Alzheimer's disease.

Medicine	Mechanism of action	Adverse effects	Used to treat mild to moderate disease	Used to treat moderate to severe disease
Donepezil	Acetylcholinesterase inhibitors: help prevent the breakdown of acetylcholine which may be needed for memory and thinking	Nausea, vomiting, diarrhea, fatigue, dizziness, drowsiness, anorexia, weight loss, confusion, insomnia	✓	✓
Rivastigmine			✓	
Galantamine			✓	
Memantine	NMDA receptor antagonist: it works by regulating glutamate. Too much glutamate can lead to brain cell death	Dizziness, headache, constipation, confusion, fatigue, vomiting, nausea, diarrhea, constipation, hypersalivation, dry mouth		✓

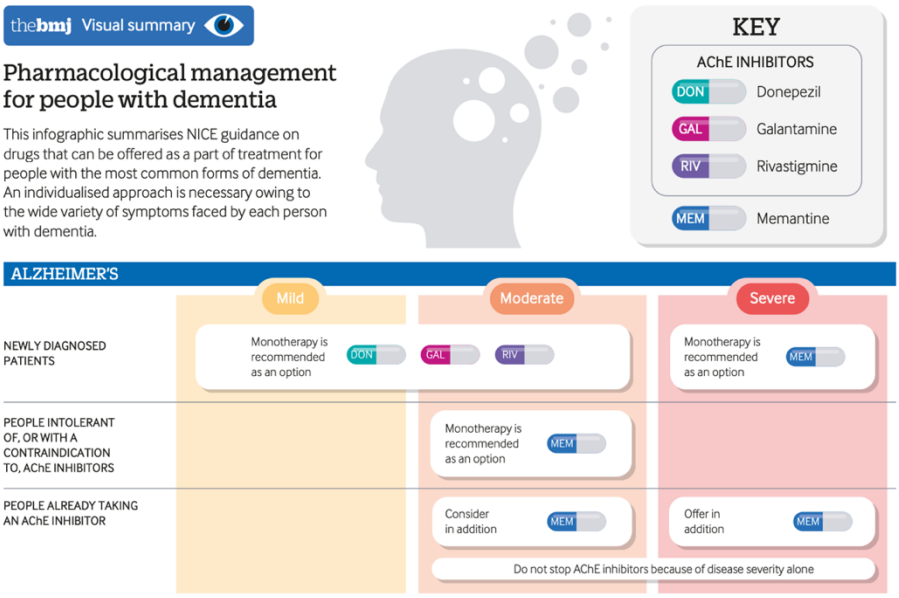

Figure 6. Pharmacological management for people with dementia (85).

Behavioural and psychiatric symptoms are highly prevalent in AD patients. These symptoms, including depression, psychosis, agitation, aggression, apathy, sleep disturbance, and reduced inhibition, are often the most challenging for individuals with dementia, their caregivers, and their healthcare providers to address (3).

Fortunately, prescribing appropriate treatment can assist in reducing or stabilizing these behavioural and psychiatric symptoms. While no drugs are currently approved by the FDA specifically for treating these symptoms, several types are utilized in clinical practice (3). The following table summarizes the main drugs used to treat the symptoms described above.

Table 3. Prescription drugs used to treat behavioural and psychiatric symptoms of AD (3).

Antidepressant medicines for low mood and irritability	**Anxiolytic** medicines for anxiety, restlessness, verbally disruptive behaviour, and resistance	**Antipsychotic** medicines for hallucinations, delusions, aggression, hostility, uncooperativeness
Citalopram Fluoxetine Paroxetine Sertraline Trazodone	Lorazepam Oxazepam	Aripiprazole Olanzapine Quetiapine Risperidone Ziprasidone Haloperidol

In response to certain behavioural disturbances, antipsychotics are usually prescribed, with quetiapine and risperidone being the most commonly used. The dosage and duration will depend on the severity of symptoms. If the main symptoms revolve around mood disturbances, antidepressant drugs such as citalopram, sertraline, or trazodone may be indicated. Generally, the use of anxiolytics or sedatives from the benzodiazepine family (such as lorazepam, potassium clorazepate, or diazepam) is not recommended, as they can worsen disorientation, lead to dependence, and, in the long term, are associated with a higher risk of cognitive decline. Nonetheless, it is ultimately the responsibility of the attending physician to assess and determine the most suitable medication for each individual case (86).

Recently, the FDA approved **Aducanumab**, a monoclonal antibody which is the first medication that aims at treating AD by targeting one of the causes of the disease, namely Aß. As the incidence of AD continues to increase annually, there is an urgent need to enhance our comprehension of non-amyloid components and their role in AD pathogenesis. Such new insight may help to identify novel pathways that can be targeted in novel AD therapies (17).

Another potential treatment in the early stages of AD could be **Lecanemab**, which slows down the cognitive and functional decline in individuals by 27%. It is a monoclonal antibody that works by targeting the elimination of specific ß-amyloid protein species in the brains of AD patients. In January 2023, the drug received the emergency authorization from the FDA, and by July 2023, it obtained standard approval. Currently, it is under review by the EMA for authorization in Europe (87).

However, developing effective drugs is challenging due to the incomplete understanding of the mechanisms underlying AD pathogenesis. As AD is a multifactorial disease, the approach to AD therapy has shifted from targeting single factors, primarily amyloid-centric, to developing drugs that address multiple aspects of the disease. Additionally, there has been a transition from treating AD at later stages of disease progression to focusing on preventive strategies at early stages of disease development, which encompass symptomatic treatments, lifestyle

modifications, and risk factor management (8). Modulating risk factors and intervening with immune mechanisms are likely to lead to future preventive or therapeutic strategies for AD (6).

New therapeutic strategies, such as plasma exchange and hemapheresis with albumin and intravenous immunoglobulin, have emerged. The positive results from these therapies in Alzheimer's disease have led to the design of the AMBAR (Alzheimer Management By Albumin Replacement) study. This study combines plasma exchange and hemapheresis with albumin and intravenous immunoglobulin in a multicenter, randomized, blind placebo-controlled parallel-group study aimed at evaluating cognitive, behavioral, and functional changes in patients with mild to moderate AD, potentially offering new therapeutic perspectives.

Conclusions.

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1. **Chronic inflammation**, as in other pathologies, appears to affect the pathophysiology of Alzheimer's disease, possibly acting as a risk factor in its development. Thus, chronic inflammation impacts various factors related to Alzheimer's disease, such as the functioning of microglial cells, activating them and causing a subsequent activation of cells like astrocytes, which collectively influence the disease's pathophysiology by achieving a pro-inflammatory state. In this way, chronic inflammation also influences processes typically associated with the disease's pathophysiology, such as the accumulation of the Aß peptide and the induction of tau phosphorylation.

2. Factors like **aging** also condition the proper functioning of cells and brain structures, leading to a concept known as **immunosenescence**, which can also condition the state of the pathology.

3. **Genetic factors** related to a higher risk of Alzheimer's disease development are also related to chronic inflammation.

4. The **microbiota** in a state of dysbiosis generates inflammation at the intestinal level, perpetuating levels of inflammatory markers and favouring a chronic inflammatory state that could influence the pathology's condition.

5. Due to the clear projection of an increase in the prevalence of Alzheimer's disease, favoured by the increase in life expectancy of the population, the need to identify possible prevention factors becomes more apparent. Therefore, following a **Mediterranean diet** or other types of dietary patterns considered healthy, such as the **MIND die**t, in addition to **physical exercise**, could be related to a lower presence of chronic inflammation and, consequently, a lower incidence of Alzheimer's disease.

6. The results obtained from the evaluation of the effect of various types of **supplementations** in patients already diagnosed with Alzheimer's disease needs to be considered as a possible way to influence the progression and evolution of the disease's effects. Therefore, despite the **promising pharmacological advances** of the latest therapies discovered, possible dietary interventions or supplementation could be key to the proper management of this devastating disease that as of today has no cure.

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