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Unraveling the impact of Omega-3 polyunsaturated fatty acids on blood-brain barrier (BBB) integrity and glymphatic function

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ABSTRACT

Alzheimer's disease (AD) and other forms of dementia represent major public health challenges but effective therapeutic options are limited. Pathological brain aging is associated with microvascular changes and impaired clearance systems. The application of omega-3 polyunsaturated fatty acids (n-3 or omega-3 PUFAs) is one of the most promising nutritional interventions in neurodegenerative disorders from epidemiological data, clinical and pre-clinical studies. As essential components of neuronal membranes, n-3 PUFAs have shown neuroprotection and anti-inflammatory effects, as well as modulatory effects through microvascular pathophysiology, amyloid-beta (Aβ) clearance and glymphatic pathways. This review meticulously explores these underlying mechanisms that contribute to the beneficial effects of n-3 PUFAs against AD and dementia, synthesizing evidence from both animal and interventional studies.

1. Introduction

Microvascular pathology, encompassing cerebral small vessel disease (cSVD) and alterations in blood–brain barrier (BBB) integrity, has been implicated in the pathogenesis of various forms of dementia, including Alzheimer's disease (AD) and vascular dementia (VaD) (Bowman et al., 2018; Forsberg et al., 2018; Kalaria, 2018; Kril et al., 2002; Zenaro et al., 2017). Additionally, the glymphatic system, a waste clearance pathway within the brain, has gained increasing attention for its potential involvement in dementia-related protein accumulation and cognitive decline (Lohela et al., 2022; Nedergaard and Goldman, 2020). Although the precise mechanisms underlying dementia and AD remain elusive, emerging research has shed light on the role of microvascular pathology and the glymphatic system in its development and progression (Di Marco et al., 2015; Hollocks et al., 2015; Köhler et al., 2015; Lin et al., 2022b; Nedergaard and Goldman, 2020; Xekardaki et al., 2012). Apart from these, AD and other dementias pathophysiology are typically associated with the accumulation of beta-amyloid plaques and tau tangles in the brain, leading to neuronal death (Long and Holtzman, 2019; Selkoe, 2002). The exact mechanisms leading to neuronal damage and death are not entirely understood, but these pathological hallmarks play a crucial role. Despite extensive research, the precise causes of these diseases remain largely unknown, and no definitive cure exists. The devastating impact of these neurodegenerative diseases extends beyond the affected individuals to families, caregivers, and society, highlighting the urgent need for effective prevention and treatment strategies.

In light of these challenges, researchers have focused on lifestyle modifications, including diet, in preventing and managing these diseases. Emerging evidence suggests that dietary factors can influence brain health and cognitive function, offering a promising avenue for intervention (Morris, 2016). Among these, omega-3 polyunsaturated fatty acids (n-3 PUFAs) have emerged as a potential key player in offering protective effects against neurodegenerative diseases, including AD and other forms of dementia, evidenced by epidemiological data, clinical and pre-clinical studies (Chang and Su, 2020; Chiu et al., 2008; Lin et al., 2022a; Luo et al., 2014; Luo et al., 2018; Song et al., 2016; Yan

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et al., 2020). Various mechanisms have been suggested, such as reducing neuroinflammation, modulating neurotransmission, and promoting neurogenesis and neuronal survival (Luchtman and Song, 2013). However, the molecular mechanisms underpinning these effects and the potential therapeutic implications require further exploration.

Ultimately, this review aims to investigate the underlying biochemical and neurophysiological mechanisms by which n-3 PUFAs might alleviate microvascular and glymphatic dysfunction (clearance of wasters) linked to pathological aging brains. In the subsequent sections, we also delve into the cellular and molecular mechanisms by which n-3 PUFAs may exert their neuroprotective effects. We have drawn insights from a diverse range of recent animal, observational and clinical trial studies, including those elucidating biological mechanisms. We also seek to address the controversies surrounding the efficacy of n-3 PUFAs in dementia prevention and treatment. Lastly, we discuss future research directions to translate these findings into practical dietary recommendations and therapeutic interventions.

2. Cerebrovascular pathologies in Dementia and AD

Neurodegenerative diseases, particularly dementia and AD, represent a significant global health challenge, with their prevalence steadily increasing due to an aging population (WHO, 2023). The three principal neuropathological processes associated with AD are the formation of neurofibrillary tangles (NFTs) due to the hyperphosphorylation of tau proteins, the accumulation of amyloid-beta (Aβ) plaques in the extracellular matrix, and neuronal death from these activities. The most common form of dementia is VaD), resulting from brain damage due to reduced or blocked blood flow to the brain, accounting for 15–25 % of all dementia cases, stands as the second most prevalent cause of dementia after AD, underscoring the urgent need for efficacious treatments (Wolters and Ikram, 2019). Followed by dementia with Lewy bodies (DLB), characterized by abnormal protein deposits in the brain known as Lewy bodies, Parkinson's disease dementia (PDD), frontotemporal dementia (FTD) and prion disease (Elahi and Miller, 2017; McKeith et al., 2017).

VaD's distinct clinical characteristics encompass a spectrum of neurocognitive deficiencies, including executive task management, language, memory, visuospatial skills, behavioral and motor abnormalities, along with depression and apathy (Sun, 2018). Complicating the scenario, VaD exhibits an elevated mortality rate, primarily due to cardiovascular and cerebrovascular complications, with a median survival of 3–5 years (Kua et al., 2014). Two salient risk factors of VaD are aging and vascular defects. Several vascular lesions, such as Chronic Cerebral Hypoperfusion (CCH), small vessel disease (manifested as leukoaraiosis and lacunar infarcts), microinfarcts, microhemorrhages, cerebral amyloid angiopathy (CAA), and mixed vascular lesions, can initiate the molecular cascade leading to VaD (Iadecola, 2013; Kalaria, 2018). Cerebral microinfarcts are abundantly detected in the brain of patients with mild cognitive impairment (MCI) (Jellinger, 2013; Rodriguez Garcia and Rodriguez Garcia, 2015). cSVD has emerged as a significant potential cause of cognitive impairment, garnering international attention. The prime manifestation of cSVD is ischemic stroke or cerebral ischemic injury, contributing significantly to VaD (Kalaria, 2018). Characterized by cerebral blood vessel constriction, cSVD can induce ischemic and hemorrhagic stroke, thereby precipitating cognitive decline and dementia (Bordes et al., 2022). Neuroimaging attributes of cSVD include small subcortical infarcts, lacunes, white matter hyperintensities, perivascular spaces, microbleeds, and brain atrophy. As a result, decreased cerebral blood flow (CBF), impaired cerebral autoregulation, endothelial dysfunction, and subsequent leakage of the BBB are observed. Small arteriosclerosis and cerebral small vessel atherosclerosis constitute the most prevalent pathological alterations associated with cSVD, exacerbating with age and under specific conditions, such as diabetes and hypertension (Li et al., 2018).

The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) guidelines delineate four primary subtypes of VaD: Post-Stroke Dementia (PSD), Subcortical Ischemic Vascular Dementia (SIVD), Multiple Infarcts (cortical) dementia (MID), and mixed dementia (Skrobot et al., 2018). PSD refers to the manifestation of dementia within six months following a stroke. SIVD, on the other hand, is attributable to alterations in small intracranial vessels. MID predominantly arises from multiple extensive cortical infarcts, which are the result of macrovascular disease. Mixed dementia is employed when patients with AD or DLB exhibit other concurrent pathological conditions (Iadecola et al., 2019).

The pathological hallmarks of FTD encompass neuronal loss, gliosis, and microvacuolar changes in the frontal lobes, anterior temporal lobes, anterior cingulate cortex, and insular cortex. These changes are associated with frontotemporal lobar degeneration, often involving tau proteins (termed tauopathies), Transactive response DNA binding protein 43 kDa (TDP-43), and FET-related proteins (Boeve et al., 2022). FTD is typically accompanied by early onset behavioral and executive complications, increasingly pronounced speech, grammar, and lexical generation deficiencies, and deterioration in semantic comprehension and nomenclature (Bang et al., 2015). DLB is typified by a broad array of neuropsychiatric manifestations, encompassing irrational behaviors, fluctuations in cognitive abilities, hallucinations, early onset cognitive degeneration, and mild indications of parkinsonism (McKeith, 2007; Tsuboi and Dickson, 2005). DLB's pathological signature is the pervasive accumulation of α-synuclein (α-Syn) in Lewy bodies and Lewy neurites within the brainstem, limbic system, and cortical regions (Tsuboi and Dickson, 2005).

AD, VaD, DLB, PDD, FTD, and prion disease are all associated with distinct neuropathological processes, yet they share the common outcome of cognitive impairment and functional decline. VaD, in particular, is recognized for its multifaceted clinical characteristics and elevated mortality rate. FTD and DLB, too, have distinct pathological hallmarks, often involving abnormal protein accumulations. Continued research is paramount to improve understanding of these diseases and to develop effective therapeutic strategies. With the aging population, there is an ever-growing need for such efficacious treatments, highlighting the urgency and importance of research in this field.

3. Understanding the brain clearance systems in Dementia and AD

The glymphatic system plays a crucial role in maintaining brain health by facilitating the clearance of metabolic waste products (Iliff et al., 2012; Jessen et al., 2015). Interestingly, studies have demonstrated that the glymphatic system is primarily active during sleep, drawing a novel link between sleep disorders and neurodegenerative diseases, including dementia and AD. Recent studies have demonstrated that during AD progression, glymphatic system function is compromised, leading to reduced clearance of Aβ and tau proteins, providing a novel framework for understanding the pathophysiology of neurodegenerative diseases (Xie et al., 2013). These proteins are key pathological hallmarks of AD, contributing to forming plaques and neurofibrillary tangles, respectively, which disrupt neuronal function and ultimately lead to cognitive decline (Mawuenyega et al., 2010). Investigations conducted on murine models have demonstrated that the suppression of aquaporin-4 (AQP4), a vital protein integral to the functioning of the glymphatic system and the regulation of cerebrospinal fluid (CSF) and interstitial fluid (ISF) flow, leads to a reduction in tau clearance, as evidenced by the research carried out by Harrison et al (Harrison et al., 2020).

Moreover, a study by Simon et al. (Simon et al., 2022) noted that a reduction in AQP4 localization in the perivascular area correlated with an increase in Aβ and neurofibrillary pathology, alongside a subsequent decline in cognitive function. These findings bolster the proposition that the pharmacological manipulation of AQP4 may represent a viable therapeutic strategy for the regulation of the glymphatic system in

dementia linked with amyloid or tau pathology, inclusive of AD. A retrospective clinical study demonstrated elevated levels of AQP4 in the CSF of patients with varying types of dementia compared to healthy counterparts. Moreover, AQP4 reveals a strong correlation with tau, a well-established marker of neurodegeneration (Arighi et al., 2022). A postmortem brain study showed a noticeable reduction in perivascular AQP4 localization. This decrease in localization was strongly correlated with an escalation in neurofibrillary and Aβ pathology. Notably, this association persisted even when accounting for the influence of age on AD pathology (Zeppenfeld et al., 2017).

Disruptions in the cerebral microvascular system, a critical part of the brain's intricate network, play a vital role in the overall functioning of the CNS and can lead to hypoxia, decreased CBF, and BBB breakdown, potentially contributing to neuronal damage. These microvascular disruptions are emerging as significant contributors to the development and progression of dementia and AD (Kisler et al., 2017; Sweeney et al., 2018). Studies have shown reduced CBF in early AD and MCI, likely resulting from neurovascular uncoupling. Moreover, hypoxia resulting from reduced CBF can lead to neuronal dysfunction and damage, contributing to cognitive decline (Iturria-Medina et al., 2016). A preclinical study with APP/PS1 transgenic mouse model showed that CAA was not simply a consequence of compromised perivascular clearance. Instead, it appears to actively contribute to this impairment, inciting alterations in arterial function and structure and thereby exacerbating the severity of AD (Kim et al., 2020).

The BBB serves as a selectively permeable border, preventing the free passage of substances from the bloodstream into the brain, thus maintaining CNS homeostasis. This selective permeability is crucial in regulating the entry and exit of molecules, ions, and cells, safeguarding the brain from potentially harmful substances and pathogens, and facilitating the clearance of waste products (Daneman and Prat, 2015). Further, BBB dysfunction may facilitate the entry of neurotoxic blood-derived products, inflammatory cells, and pathogens into the brain. It may also lead to impaired clearance of Aβ, promoting its accumulation in the brain. Notably, chronic inflammation triggered by BBB disruption can further aggravate the disease, contributing to a vicious cycle of neurodegeneration (Zlokovic, 2011). Specifically, in AD, BBB breakdown could lead to the accumulation of neurotoxic proteins, increased neuroinflammation, and neuronal injury, thereby exacerbating cognitive decline (Nation et al., 2019). Altogether, the evidence suggests a significant role of brain clearance system dysfunction in dementia and AD, highlighting the importance of further investigations in this field. Understanding the exact mechanisms and identifying potential therapeutic targets could pave the way for innovative strategies to combat these devastating disorders.

4. N-3 Polyunsaturated fatty acids (PUFAs) in neurodegenerative diseases

N-3 PUFAs play a crucial role in various biological functions. Docosahexaenoic acid (DHA), a key component of neuronal membranes, maintains membrane fluidity, modulates neurotransmission, and promotes neuronal survival (Crawford et al., 1999). In contrast, eicosapentaenoic acid (EPA) serves as a substrate for producing eicosanoids and other bioactive mediators, contributing to anti-inflammatory responses and cardiovascular health (Shearer et al., 2012). Emerging research reveals the significant role of n-3 PUFAs in generating specialized pro-resolving lipid mediators, which actively promote the resolution of inflammation, suggesting their potential implication in neuroinflammatory conditions like AD (Serhan, 2014). Regarding neurodegenerative diseases, n-3 PUFAs have shown potential in AD and dementia. They are believed to exert neuroprotective effects, influencing neuroplasticity and neurogenesis, which are vital for cognitive function (Dyall, 2015).

Moreover, an inadequate intake or deficits in circulating levels of these fatty acids may influence neurodegenerative processes (Salem et al., 2001a). Several studies have reported reduced levels of n-3 PUFAs, notably DHA, in the brains and plasma of AD and dementia patients. For instance, Cunnane et al. (2012) discovered significantly lower concentrations of DHA in the hippocampus – a brain region integral to memory and heavily affected in AD – in patients with AD compared to healthy controls (Cunnane et al., 2009). A prospective clinical study conducted on elderly patients diagnosed with AD found a correlation between lower baseline levels of DHA and an increased risk of cognitive deterioration (Chu et al., 2022).

Furthermore, a population-based study of the association between fatty acid plasma levels and dementia risk in a cohort of over 1200 elderly individuals discovered that individuals with the highest plasma levels of DHA had a 47 % lower risk of developing dementia over nine years compared to those with the lowest levels (Schaefer et al., 2006). Another case-control study conducted by (Conquer et al., 2000) found that plasma concentrations of DHA and total n-3 PUFAs were significantly lower in AD patients than in control subjects. This deficiency was more pronounced in patients with severe AD, suggesting a possible correlation between n-3 PUFA levels and disease severity. In addition to empirical studies, *meta*-analyses have further emphasized this link. A *meta*-analysis by Zhang et al. (Zhang et al., 2016b) comprising 21 studies with over 26,000 participants found that higher dietary intake of n-3 PUFAs was associated with a reduced risk of AD. Similarly, a *meta*-analysis by Pan et al. (Pan et al., 2015) involving over 180,000 participants observed a significant association between higher fish (a primary source of n-3 PUFAs) consumption and reduced AD risk.

Despite this mounting evidence, the therapeutic potential of n-3 PUFA supplementation in AD and dementia patients remains a subject of ongoing debate (Dacks et al., 2013). A comprehensive prospective cohort study involving 215,083 participants conducted in the United Kingdom from 2006 to 2010 investigated the correlation between fish oil (FO) supplementation and the risk of dementia. The findings substantiated the hypothesis that routine consumption of FO may reduce the likelihood of dementia onset in older individuals. However, the study could not conclusively link FO intake with the risk of specific dementia subtypes due to the limited number of cases within each subtype. Furthermore, no significant interaction was found between FO intake and the incidence of dementia among individuals with different apolipoprotein E (ApoE) genotypes (Liu et al., 2022). A *meta*-analysis posits that moderate fish consumption can act as a preventative measure against ischemic stroke (He et al., 2004). Research conducted by De Goede et al. identified a correlation between elevated levels of DHA and a reduced risk of stroke in women, although these associations did not reach statistical significance in men (de Goede et al., 2012). Several studies have suggested that individuals who consume fish at least once a week may experience a lower risk of stroke (Gillum et al., 1996; Keli et al., 1994).

While some clinical trials have reported positive effects on cognitive function (Frangou et al., 2006), others have not found significant benefits (Quinn et al., 2010). For instance, a study by Whalley et al. (Whalley et al., 2008) revealed that, in a cohort of older individuals in Scotland, lower intake of dietary n-3 PUFAs was associated with cognitive decline over three years. Some clinical trials have found a slow decline in cognitive function with n-3 PUFA supplementation, although more research is needed to establish firm recommendations (Andrieu et al., 2017). Whereas Thomas et al. (Thomas et al., 2020) discovered that higher consumption of EPA and DHA was linked to a reduced incidence of dementia and a decelerated decline in global cognition, memory, and medial temporal lobe brain volume. These conflicting results (Burckhardt et al., 2016) might be attributed to variations in trial design, including dosage, duration, and the stage of disease at the time of intervention. In essence, an accumulating body of evidence suggests a potential link between low levels of n-3 PUFAs and an increased risk of AD and dementia. Moreover, the potential of n-3 PUFAs for therapeutic supplementation is vast, spanning from cardiovascular health to mental health and neurodegenerative diseases, metabolic disorders, and

potentially even cancer. As science unravels their complex biological roles, their potential in preventive and therapeutic strategies continues to grow. However, given the complexity of human health and disease, a careful and balanced approach is needed to understand their full potential and limitations.

5. Mechanisms of action of n-3 PUFAs in the brain clearance systems

N-3 PUFAs have been widely studied for their role in brain health and disease, and several lines of research suggest their potential neuroprotective actions. Emerging evidence suggests that n-3 PUFAs may have potential therapeutic benefits in dementia *via* brain clearance systems. Animal and clinical trials have also examined the effects of n-3 PUFAs in other types of dementia.

5.1. Clinical evidence

Given the complexity of cerebrovascular diseases and our limited understanding of the underlying molecular and cellular processes, there is a dearth of clinical studies examining the efficacy of n-3PUFAs brain clearance systems on VaD. Despite this, research has been conducted on the effects of n-3 PUFAs and their components on VaD risk factors, including white matter lesions, ischemic stroke, decreased blood pressure, reduced platelet aggregation, increased deformability of erythrocyte cells, and cSVD (Clarke et al., 2005; Iso et al., 2002). In a recent cohort study on deceased participants in the Rush Memory and Aging Project (MAP), the consumption of seafood and long-chain n-3 PUFAs demonstrated no association with the presence of cerebral infarcts or Lewy bodies. Conversely, an elevated intake of α-linolenic acid, a shorter-chain n-3 fatty acid predominantly found in plant sources, was linked to a reduced likelihood of cerebral infarcts (Morris et al., 2016). A *meta*-analysis has suggested that higher consumption of n-3 PUFAs reduces morbidity and mortality associated with body mass index (BMI) and sex, as well as the overall risk of stroke (Cheng et al., 2015). It has also been demonstrated that marine n-3 PUFAs can mitigate risk factors for cardiovascular diseases (CVDs), such as hyperlipidemia (Fruchart et al., 2008), hypertension (Mano et al., 1995), and type 2 diabetes (Manoria et al., 2013). This is achieved *via* potential mediators of lipid-induced serum soluble intercellular adhesion molecule type 1 (sICAM-1) (Kooshki et al., 2011), insulin resistance, and inflammation (Lankinen et al., 2009). Both clinical and preclinical studies have indicated that a combination of parent fatty acid alpha-linolenic acid (ALA) combined with EPA and DHA offers superior benefits compared to individual PUFAs in insulin-sensitive tissues, insulin resistance, and vascular dysfunction (Robbez Masson et al., 2008). Other evidence has emerged supporting the protective role of n-3 PUFAs in VD, including the activation of ATP-sensitive $K^{(+)}$ channels, which in turn stimulate the enzyme nitric oxide synthase (eNOS) (Nirwane et al., 2015).

According to a series of cross-sectional studies, there exists a robust correlation between WMH and EPA (Song et al., 2015), DHA (Bowman et al., 2013; Song et al., 2015; Tan et al., 2012), a combination of DHA and EPA(Song et al., 2015), and the ratio of EPA to AA (Nagai et al., 2015; Suwa et al., 2015). Nonetheless, no significant associations were found between WMH and the n-3 PUFAs examined in red blood cells (RBC), as indicated by both cross-sectional and prospective studies. A study exploring the effect of n-3 PUFAs and their constituents on stroke or cSVDs incorporated a sample of 1,057 individuals diagnosed with atrial fibrillation (AF) in Switzerland between 2014 and 2017. The analysis of individual and total n-3 PUFAs revealed no substantial link with markers of SVD. Crucially, there was no significant association between total n-3 PUFAs and large non-cortical or cortical infarcts (LNCCI). However, EPA was found to be inversely related to LNCCI, while DPA was associated with a higher incidence of LNCCI (Reiner et al., 2021). Despite the proven preventative impact of n-3 PUFAs on high-risk factors for VaD, its direct influence of n-3 PUFAs on VaD remains highly contentious due to inconsistent study results and a lack of research specifically targeting VaD. As such, the need for more uniform research and *meta*-analysis is evident in order to bolster the evidence supporting the use of n-3 PUFAs as a preventative or therapeutic intervention in clinical settings. Table 1 provides a summary of the research findings relating to n-3 PUFAs in clinical trials focused on VaD.

5.2. Preclinical evidence

N-3 PUFAs have been recognized for their capability to boost cerebral angiogenesis (Wang et al., 2014), offering protection against cardiovascular and cerebrovascular anomalies. N-3 PUFAs, DHA and EPA, have been shown to induce blood pressure reduction and vasodilation. This physiological effect is mediated through the activation of large conductance calcium-activated potassium (K) channels (BKCa), ATP-sensitive K channels (KATP), and possibly members of the Kv7 family of voltage-activated K channels, leading to hyperpolarization and relaxation (Bercea et al., 2021). Moreover, the influence of n-3 PUFAs on the expression of adhesion molecules by endothelial cells (ECs) minimizes leukocyte infiltration into the vascular wall, thereby fostering vascular health (Baker et al., 2018). A study has also connected DHA consumption to enhanced cerebrovascular health and a plethora of positive brain neuroimaging phenotypes (Sala-Vila et al., 2021).

Preliminary animal studies suggest that DHA may counteract hypertension and VaD by improving central nervous system functionality, mainly by enhancing reduced acetylcholine levels in the brain of stroke-prone, spontaneously hypertensive rats (Kimura et al., 2002). One study unveiled an association between low levels of plasma n-3 PUFAs and pathologies of cSVDs (Song et al., 2015). However, the potential of n-3 PUFAs intake in mitigating brain SVDs pathology warrants further investigation. In patients with atrial fibrillation (AF), an inverse relationship was identified between EPA levels and the incidence of ischemic brain infarcts, although this correlation was not observed with indicators of SVD (Reiner et al., 2021). Documentation suggests an inverse correlation between the intake of oily fish and the severity of cSVD biomarkers, such as white matter hyperintensity (WMH) (Del Brutto et al., 2022; Del Brutto et al., 2021). Further research is indispensable to assess whether the intake of oily fish could decrease the incidence of cSVD-related VaD.

A growing body of research indicates that n-3 PUFAs possess neuroprotective effects in instances of stroke and vascular injury. Cross-sectional studies have revealed a correlation between low n-3 PUFAs levels and increased risk for acute ischemic and hemorrhagic stroke, particularly among Asian populations (Song et al., 2015). The Middle Cerebral Artery Occlusion (MCAO) animal model, which induces transient focal cerebral ischemia, has been employed to verify the neuroprotective properties of n-3 PUFAs. A three-month DHA treatment mitigated acute immune response/brain damage following ischemic injury, which was achieved by inhibiting microglial activation, reducing the size of the ischemic lesion, and elevating the levels of the anti-apoptotic molecule B-cell lymphoma 2 (Bcl-2) in the brain (Lalancette-Hébert et al., 2011). Further studies showed that intravenous injection of n-3 PUFA lipid emulsion (OGV) lessened the stroke's extent and severity, restored mitochondrial function, curtailed the excitotoxic release of glutamate, and suppressed inflammatory markers such as Cyclooxygenase-2 (COX-2) and interleukin (IL)-6. Notably, the therapeutic efficacy of acute OGV administration was optimal when given soon after stroke induction, suggesting potential enhancement of short-term neurological outcomes (Berressem et al., 2016).

Moreover, a diet rich in n-3 PUFAs improved motor function and neurological performance in ischemic mice, compared to those on a low-fat, saturated fatty acid-rich diet (LFD or HFD-SFA) (Gonzalo-Gobernado et al., 2019). A post-stroke n-3 PUFA regimen, specifically DHA or a combination with FO, was administered 60 min post-MCAO for 14 days, showing protection against gray matter neuronal loss and promotion of white matter integrity, thereby facilitating long-term sensorimotor

Table 1
Summary of research findings on n-3 PUFAs in Vascular dementia-related clinic trails.

Trial category	Name	Participants	Period	Number	Evaluation Metrics	Findings	Reference
A randomized, double-blind, placebo-controlled 2 × 2 factorial trial	Vitamin D and/or n-3 PUFAs supplements	Men over 50 and women over 55 with no history of cancer, myocardial infarction, stroke, transient ischemic attack, or coronary revascularization.	5.3 years	290	Stroke events, post-stroke physical performance scale and disability events detection.	Randomized pre-stroke n-3 PUFAs supplementation did not significantly improve post-stroke outcomes in middle-aged and older adults.	(Rist et al., 2021)
A multicenter, randomized, double-blind, placebo-controlled, secondary prevention trial	5-methyltetrahydrofolate and vitamins B-6 and B-12, EPA and DHA (2: 1) , B vitamins and n-3 PUFAs	Men and women aged 45–80 with recent myocardial infarction (MI), unstable angina, or ischemic stroke	4 years	1748	Cognitive function assay.	No significant main effects of group assignment on cognitive function were found; however, in the subgroup with prior stroke, for example, participants assigned to receive B vitamins plus n-3 PUFAs were significantly less likely to have a decreased score on the temporal orientation task than were those assigned to receive placebo.	(Andreeva et al., 2011)
A prospective randomized open-label, blinded endpoint trial	EPA	Hypercholesterolemic patients with serum total cholesterol ≥ 6.5 mmol/L (males 40 to 75 years, women postmenopausal to 75 years)	5 years	18,644	Stroke occurrence and fatty acid analysis.	High-purity EPA appears to reduce the risk of recurrent stroke in a Japanese population of hypercholesterolemic patients receiving low-dose statins.	(Tanaka et al., 2008)
A randomized, double-blind, placebo-controlled clinical trial	Antioxidants, n-3 PUFAs and antioxidants plus n-3 PUFAs	Stroke patients admitted to rehabilitation hospital with sequelae of first ischemic stroke	6 and 12 months	72	Clinical events assay.	The study observed a trend towards lower mortality in the subgroup treated with n-3 fatty acids, but there was no significant difference in rehabilitation outcome status between groups.	(Garbagnati et al., 2009)
A cross-sectional study	EPA,DHA,DPA,ALA and n-3 PUFAs	Atrial fibrillation (AF) patients	3 years	1657	Ischemic cerebral infarct size LNCCI, microbleed number SNCI and white matter lesion (WML) volume assessment.	Neither individual nor total n-3 FA were associated with markers of small vessel disease. DHA, ALA and total n-3 FA were not associated with LNCCI. EPA is inversely associated with prevalence of LNCCI. DPA is associated with higher prevalence of LNCCI	(Reiner et al., 2021)
A longitudinal prospective study	Oily fish	Individuals of Amerindian ancestry aged ⩾60 years	6.5 years	263	White matter hyperintensity (WMH) assessment.	An inverse relationship exists between oily fish intake and WMH progression.	(Del Brutto et al., 2022)
A Population-Based Study	Oily Fish	Community-dwellers aged ≥ 60 years living in three neighboring rural villages of coastal Ecuador	6 months	572	Cerebral small vessel disease (cSVD) biomarkers, including white matter hyperintensities (WMH) assessment.	Increased intake of oily fish was inversely associated with WMH severity.	(Del Brutto et al., 2021)

recovery in a mouse model (Jiang et al., 2016). In addition, long-term stroke outcomes were assessed concerning n-3 PUFA supplementation alone and in combination with DHA in the MCAO mouse model, suggesting an efficacious treatment protocol for fostering neurovascular regeneration and long-term cognitive enhancement (Pu et al., 2016). Overall, the protective roles of n-3 PUFAs in animal models have been extensively examined and validated in both ischemia–reperfusion (Cai et al., 2018; Cao et al., 2021; Zhang et al., 2014; Zhang et al., 2015) and permanent ischemia models (Chang et al., 2013), as well as in pre- (Chang et al., 2013; Ren et al., 2019) and post-modeling interventions (Cai et al., 2018; Cao et al., 2021; Zhang et al., 2014; Zhang et al., 2015).

The majority of previous investigations into the impact of n-3 PUFAs have primarily employed the MCAO models. Our research team has innovated two new models to imitate Subcortical Ischemic Vascular Dementia (SIVD) and Multiple Infarct (cortical) Dementia to elucidate the effects of n-3 PUFAs. Initially, we designed a mouse model of small focal cortical infarcts (FCI) by disrupting the target *via* the endothelium of arterioles using concentrated femtosecond laser pulses. This micro-ischemic model demonstrated functional deficits *via* the occlusion of the distal branch of the middle cerebral artery and all its leptomeningeal anastomosis, enabling us to investigate the impact of n-3 PUFAs on ischemic injury *in vivo*. Our results indicated that n-3 PUFAs ameliorated functional and physical impairments in mice following FCI damage (Shi et al., 2016). In a pioneering move, our research team employed a brain micropeduncle animal model to examine the effect of n-3 PUFAs on microinfarction. In C57BL/6 and Fat-1 mice, we obstructed cortical penetrating arterioles using concentrated femtosecond laser pulses to develop a single microinfarct model, and we induced numerous diffuse cerebral microinfarcts by administering cholesterol crystals into the right internal carotid artery. By metabolizing n-6 PUFAs into n-3 PUFAs in Fat-1 mice and providing a FO diet to C57BL/6 mice three weeks prior, we established for the first time that both exogenous delivery and endogenous production of n-3 PUFAs exhibit preventive properties on microinfarction. This occurs by inhibiting cell apoptosis and limiting

tissue damage, thus ameliorating cognitive impairment (Luo et al., 2018).

Several mechanisms have been proposed through which n-3 PUFAs ameliorate VaD potentially including the inhibition of inflammation and oxidative stress, remediation of mitochondrial dysfunction (Cao et al., 2021), promotion of angiogenesis (Wang et al., 2014), and facilitation of endogenous brain repair (Pu et al., 2017). These mechanisms also involve the preservation of CBF (Kaufman et al., 2020), reducing scar formation, and improving white matter integrity (Pu et al., 2016). Zendedel and colleagues reported a significant reduction in cortical infarct volume and behavioral impairments due to decreased neuroinflammation in the cortical penumbra. They also noted a shift in microglia in the penumbra from the destructive M1- to the protective M2 phenotype in response to n-3 PUFAs administration (Zendedel et al., 2015). Cai et al. illustrated the impact of n-3 PUFAs on immune cells. They observed that systemic DHA treatment significantly inhibited immune cell infiltration and promoted macrophage polarization towards the anti-inflammatory M2 phenotype in the ischemic brain. Furthermore, following ischemic stroke, systemic DHA treatment mitigated elevated pro-inflammatory markers in the blood and induced a shift in circulating macrophage polarity towards the M2 phenotype (Cai et al., 2018). Several studies have corroborated this inhibitory effect on neuroinflammation (Chang et al., 2013; Gonzalo-Gobernado et al., 2019; Jiang et al., 2016; Lalancette-Hébert et al., 2011).

Zhang et al. discovered that n-3 PUFAs protect the brain from ischemic injury by elevating 4-hydroxyhexenal (4-HHE) production, activating nuclear factor-erythroid factor 2-related factor 2 (Nrf2), and upregulating heme oxygenase-1 (HO-1) (Zhang et al., 2014). These findings align with outcomes from a rat model of permanent cerebral ischemia. Here, DHA mitigated post-stroke oxidative stress, c-Jun N-terminal kinase (JNK) phosphorylation, c-Jun phosphorylation, and activating protein-1 (AP-1) activation while concurrently enhancing ischemia-induced Nrf2 and HO-1 expression (Chang et al., 2013). Furthermore, substantial evidence indicates that n-3 PUFAs act as a potential angiogenic promoter (Wang et al., 2014; Zhang et al., 2015), augmenting post-stroke revascularization (Wang et al., 2014) and brain repair. This includes improved white matter integrity (Pu et al., 2016), endogenous neurogenesis, oligodendrocyte production (Zhang et al., 2015), and other long-term functions (Wang et al., 2014). Table 2 summarises research findings pertaining to n-3 PUFAs in VaD-related animal models.

6. N-3 PUFAs and Blood-Brain barrier (BBB) integrity function

The phospholipid (PL) structure of the brain is enriched with n-3 PUFAs, notably DHA and arachidonic acid (ARA) (Dyall and Michael-Titus, 2008). DHA is a key constituent of PLs in various brain structures, prominently in the cerebral cortex, mitochondria, synaptosomes, and synaptic vesicles (Connor, 2000). This fatty acid augments neuronal membrane permeability, moderates the functionality of transmembrane and peripheral proteins (Fig. 1F), including receptors, enzymes, and ion channels, and supervises neurotransmitter production and activity, signal transduction, and BBB integrity (Fig. 1C) (Luchtman and Song, 2013; Yehuda et al., 2005). A diminution in n-3 PUFAs, culminating in reduced membrane fluidity (Fig. 1A), is observed in aged brain meninges, which also present elevated cholesterol levels (Fig. 1D) and alterations in BBB structure and fatty acid metabolism (Yehuda et al., 2002). DHA has been reported to enhance the permeability of cell membranes to small polar molecules due to its thinner and loosely packed DHA-rich membranes and the opposite for cholesterol-rich membranes (Fig. 1E) (Hishikawa et al., 2017). Earlier studies identified increased membrane rigidity (Fig. 1B), concurrent age-related synaptic alterations (McGahon et al., 1999), and diminished expression of efflux transporters (Yan et al., 2020) and tight junction proteins (Xie et al., 2020) at the BBB in AD rodents. Subsequently, impaired erythrocyte membrane fluidity was also detected in AD patients' brains.

The BBB transport of plasma-derived DHA modulates brain DHA levels, and it is well-recognized that orally administered n-3 PUFAs can traverse the BBB in adults (Freund Levi et al., 2014); thus, the clinical application of n-3 PUFAs in AD patients warrants further investigation. Interestingly, it is also worth noting that ApoE4 can elevate BBB permeability in either Aβ-dependent (Sperling et al., 2012) or -independent manners (Yamazaki et al., 2020). Hence, exploring the use of ApoE-directed treatments targeting the BBB in human clinical trials for AD treatment may be of significant interest. A recent longitudinal investigation employing magnetic resonance imaging (MRI) to evaluate BBB integrity (using dynamic contrast-enhanced MRI to determine K_{trans} values) revealed an inverse correlation between the long-chain n-3 score (the combined levels of DHA and EPA) and K_{trans} values in the internal capsule. This suggests that elevated n-3 PUFAs levels correspond to enhanced integrity of the BBB within this specific region (Barnes et al., 2021).

Furthermore, a diet enriched with DHA has been shown to counteract age-related membrane rigidity in the hippocampus of preclinical AD animals (McGahon et al., 1999) (Fig. 1B). Additionally, DHA improved the avoidance learning deficit in rats upon Aβ 1–40 infusion, ascribed to changes in synaptic plasma membrane fluidity (Hashimoto et al., 2006). Moreover, Ma et al. discovered that DHA alleviated AD pathology by escalating Lipoprotein Receptor 11 (LR11) content in the mouse brain membrane, which mitigated Aβ production by reducing the transport of Amyloid Precursor Protein (APP) to Aβ-producing secretase (Ma et al., 2007). Our research identified the beneficial effects of n-3 PUFAs supplementation on the BBB of AD mice, with the Lipoprotein receptor-associated protein 1 (LRP-1), a key BBB efflux transporter, significantly upregulated by FO supplementation abundant in n-3 PUFAs in APP/PS1 mice (Yan et al., 2020). Subsequently, we identified that the tight junction protein ZO-1 expression in APP/PS1 mice decreased from 5 months of age, implying an early-stage alteration in BBB integrity. Given that n-3 PUFAs supplementation can counterbalance the reduction in ZO-1 expression, it suggests that these fatty acids may offer early intervention to safeguard BBB integrity in AD (Xie et al., 2020). In neonatal mice, the administration of n-3 PUFAs demonstrated a mitigating effect on hypoxia/ischemia (H/I)-induced BBB disruption. This beneficial impact was evidenced by decreased tracer efflux and IgG extravasation, maintained the integrity of BBB ultrastructure, and upregulated expression of tight junction proteins (Zhang et al., 2016a).

7. Anti-Amyloid role of N-3 PUFAs

The link between n-3 PUFAs and a decrease in pathologies specific to AD, such as Aβ levels, is increasingly supported by scientific evidence. Numerous clinical studies have examined the impact of n-3 PUFAs on amyloid pathology in AD patients. An RCT by Tofiq et al. found that six months of n-3 fatty acid supplementation did not alter the levels of biomarkers such as Aβ38, Aβ40, Aβ42, t-tau, p-tau in CSF samples of AD patients (Tofiq et al., 2021). In contrast, a smaller clinical study indicated that changes in CSF DHA levels were inversely related to total tau and phosphorylated tau levels (Freund Levi et al., 2014). The variability in the results of these clinical trials could be attributed to differences in the participant population and the limited number of patients enrolled in these studies.

Recent studies have indicated that diminished n-3 PUFAs levels correspond to increased oligomeric Aβ in the hippocampus of rats (Morgese et al., 2020). In an early study conducted in 2005, Lim et al. provided evidence that a diet high in DHA, a type of n-3 PUFAs, notably reduced the insoluble amyloid and plaque burden in the brain tissue of APPsw (Tg2576) transgenic mouse model (Lim et al., 2005). This finding was later substantiated by Green et al., who used transgenic mice that developed both Aβ plaques and tau tangles. They discovered that a diet supplemented with DHA curtailed Aβ accumulation and diminished tau protein levels over three months. This effect was even more pronounced after nine months, particularly in the group only supplemented with

Table 2
Summary of research findings on n-3 PUFAs in Vascular dementia-related animal models.

Name	Model	Period	Evaluation Metrics	Findings	Reference
Endogenous and exogenous n-3 PUFAs	Focal cortical infarction (FCI) model	2 weeks	Infarct volume assessment, behavioral tests, ROS and GSH assay.	N-3 PUFAs improve functional and physical impairment in mice following FCI injury.	(Shi et al., 2016)
Fish oil (FO)	A single microinfarct model	3 weeks	Behavioral test, fatty acid analysis, blood flow monitoring, PI positive cells, TUNEL positive cells, microinfarct volume and apoptosis detection.	N-3 PUFAs attenuated ischemic injury induced by PAO by inhibiting apoptosis, mitigating tissue damage, and thus improving cognitive impairment.	(Luo et al., 2018)
Fish oil (FO)	Multiple diffuse microinfarcts model (MCAO)	3 weeks	Behavioral test, fatty acid analysis, blood flow monitoring, PI positive cells, TUNEL positive cells, microinfarct volume and apoptosis detection.	N-3 PUFAs confer beneficial effects in the mouse model with multiple diffuse microinfarcts	(Luo et al., 2018)
DHA/EPA	Transient middle cerebral artery occlusion (tMCAO)	48 h	Infarct volume, infarct severity and hemorrhagic transformation assessment, neurobehavioral and antioxidant enzyme activity test.	Mice fed with DHA/EPA displayed better histological outcomes after cerebral ischemia. Furthermore, PUFA-enriched diets improved the motor function and neurological performance of ischemic mice.	(Gonzalo-Gobernado et al., 2019)
ALA	Transient middle cerebral artery occlusion (tMCAO)	12 months	Cerebral ischemic lesions and behavioral test.	ALA supplements both improve spatial learning and memory after stroke.	(Bonetti et al., 2021)
DHA	Middle cerebral artery occlusion (MCAO)	3 months	Neuroinflammation evaluation, cytokine concentration and stroke area assessment.	DHA treatment prevented microglial activation after ischemic injury, reduced the size of ischemic lesions, and increased levels of the anti-apoptotic molecule Bcl-2 in the brain.	(Lalancette-Hébert et al., 2011)
Endogenous n-3 PUFAs	Transient middle cerebral artery occlusion (tMCAO)	3 weeks	Body weight change and survival rate evaluation, behavior measurement, cerebral infarction volume and revascularization of IBZ in the ischemic border zone evaluation.	Transgenic overproduction of n-3 PUFAs improved post-stroke revascularization and enhanced endogenous angiogenesis; n-3 PUFAs induced Ang 2 production in astrocytes, which subsequently promoted EC proliferation and barrier formation; Ang 2 potentiated VEGF-mediated angiogenic effects through the downstream molecules PLCγ1 and Src.	(Wang et al., 2014)
N-3 PUFAs	Transient middle cerebral artery occlusion (tMCAO)	12 and 24 h	Cortical infarct volumes and behavioral score, quantitative gene expression studies of dendritic- (GAP-43), axonal (Tau) markers, hypoxia-induced and neuroinflammatory markers and gene markers characteristic for the pro-inflammatory M1- (Arg1) and protective M2- (Trem2) microglia phenotype.	N-3 PUFAs provide solid neuroprotection in the cerebral cortex which is paralleled by a reduction of behavioral deficits. First, local neuroinflammation within the cortical penumbra is slowed down and second, the switch of local microglia in the penumbra from a devastating M1- to a more protective M2 phenotype is promoted by PUFA n3.	(Zendedel et al., 2015)
Nven 10 % ®, OGV	Transient middle cerebral artery occlusion (tMCAO)	24 h	Neurobehavioral score, infarct size and severity assessment, mitochondrial function, glucose and glutamate levels and pro-inflammatory markers detection.	N-3 PUFAs provide unique neuroprotective properties in acute focal cerebral ischemia in mice by attenuating mitochondrial dysfunction as well as neuroinflammation and excitotoxicity.	(Berressem et al., 2016)
DHA and DHA + Fish oil (FO)	Middle cerebral artery occlusion (MCAO)	14 days	Motor function test, gray and white matter damage assessment and microglial responses detection.	DHA and FO combined treatment-facilitated long-term sensorimotor recovery and demonstrated greater beneficial effect than DHA injections alone. n-3 PUFAs not only offered direct protection on white matter components, such as oligodendrocytes, but also potentiated microglial M2 polarization.	(Jiang et al., 2016)
N-3 PUFAs and n-3 PUFAs + DHA	Transient middle cerebral artery occlusion (tMCAO)	4 weeks	Behavioral test, cerebral infarct volume assessment, proliferating cell and angiogenesis test, astrocyte glial scar formation test.	FO dietary supplements combined with DHA injections provide effective and sustained protection against ischemia-induced tissue loss and functional deficits long after stroke.	(Pu et al., 2016)
N-3 PUFAs	Transient middle cerebral artery occlusion (tMCAO)	1 and 3 days	Infarct volume analysis, rotarod test, neurological scoring, astrocytes polarization assay and mitochondrial function assay.	N-3 PUFAs prevent mitochondrial dysfunction, thereby limiting A1-specific astrocyte polarization and subsequently improving the neurological outcomes of mice with ischemic stroke.	(Cao et al., 2021)
N-3 PUFAs	Transient middle cerebral artery occlusion (tMCAO)	3 months before and 35 days after tMCAO	Infarct volume and neurological function measurement, proliferating cells, vascular labeling and vascular density analysis.	N-3 PUFAs reduce infarct volume without affecting regional cerebral blood flow, improve neurological function and confer long-term cerebral ischemia neuroprotection, enhance post-ischemic revascularization in the ischemic penumbra, and stimulate angiogenesis, stimulating brain post-ischemia neurogenesis, enhanced oligodendrocyte production and white matter recovery.	(Zhang et al., 2015)

(*continued on next page*)

Table 2 (*continued*)

Name	Model	Period	Evaluation Metrics	Findings	Reference
DHA	Transient middle cerebral artery occlusion (tMCAO)	3 days	Stroke outcomes, systemic inflammatory status, and microglia/macrophage phenotypic alterations assay.	DHA ameliorates cerebral infarction and neuronal death after tMCAO, reduces immune cell infiltration into ischemic brain without altering the number of immune cells in the blood and spleen, induces regression of the inflammatory phenotype of macrophages in ischemic brain, and switches circulating macrophage polarity to anti-inflammatory inflammatory M2 phenotype	(Cai et al., 2018)
Endogenous n-3 PUFAs and Fish oil (FO)	Transgenic mice overexpressing fatty acid metabolism-1 and transient middle cerebral artery occlusion (tMCAO)	21 days	Fatty acid analysis, ischemic outcomes assessment and antioxidant function assessment.	Transgenic mice overexpressing fatty acid metabolism-1, an enzyme that converts n-6 PUFAs to n-3 PUFAs, were remarkably resistant to focal cerebral ischemia compared with their wild-type littermates. Regular mice fed with a fish oil-enhanced diet also demonstrated significant resistance to ischemia compared with mice fed with a regular diet, and that the protective mechanisms involve Nrf2 activation and HO-1 upregulation by 4-HHE.	(Zhang et al., 2014)
DHA	Transient middle cerebral artery occlusion (tMCAO)	2 weeks	Neurological function and infarct volume assessment, apoptotic cells and neuroinflammation detection.	N-3 PUFAs protect mice from focal cerebral ischemic injury by reducing inflammation and reducing apoptosis through activating GPR120 receptor.	(Ren et al., 2019)
N-3 PUFAs and ALA	Transient middle cerebral artery occlusion (tMCAO)	6 weeks	Behavioral test and cerebral ischemic lesions assessment.	Both types of supplements improve spatial learning and memory after stroke.	(Bourourou et al., 2016)
DHA	Transient middle cerebral artery occlusion (tMCAO)	7 days	Neurological status and infarct size and volume assessment.	Experimental treatment with low-dose 3.5 mg/kg and moderate-dose 7 mg/kg DHA improves neurological and histological outcomes after focal cerebral ischemia	(Belayev et al., 2009)
DHA	Permanent focal cerebral ischemia model	3 days	Ischemic infarction quantification, neurological assessment, water content assay, blood–brain barrier (BBB) permeability measurement, lipid peroxidation, reduced glutathione (GSH) and myeloperoxidase activity (MPO) measurement.	DHA exhibited neuroprotective and anti-inflammatory effects against ischemic brain injury and these effects were accompanied by decreased oxidative stress and JNK/AP-1 signaling as well as enhanced Nrf2/HO-1 expression.	(Chang et al., 2013)

DHA (Green et al., 2007). However, in the same year, Arendash et al. reported disparate results using double transgenic APP/PS1 mice. They found that a diet high in n-3 PUFAs (13 %) had no discernible impact on the soluble or insoluble levels of Aβ in the hippocampus of these mice, nor did it affect cognition or brain fatty acid levels (Arendash et al., 2007). In a differing perspective, Lebbadi et al. demonstrated that the expression of endogenous n-3 PUFAs decreases levels of soluble and insoluble phosphorylated tau and glial fibrillary acidic protein in 3 × Tg-AD mice (Lebbadi et al., 2011; Wu et al., 2016). The divergence in these findings could be attributable to the possibility that endogenously expressed n-3 PUFAs are present in higher quantities than n-3 PUFAs derived from dietary supplementation.

In light of conflicting findings, a systematic review and *meta*-analysis conducted by Hooijmans et al. provided a comprehensive review of the effects of n-3 PUFAs on cognitive impairment, Aβ pathology, and neuronal loss in AD animal models. This study revealed that long-term supplementation with n-3 PUFAs led to decreased n-6/n-3 PUFAs ratio and Aβ levels, concurrently enhancing cognitive function in mice. This effect was more marked in rats than in mice, particularly males over females (Hooijmans et al., 2012). Interestingly, early FO consumption in AD mice appeared more beneficial than mid- or later-stage interventions. Research by Jović et al. demonstrated that short-term FO supplementation during the pre-symptomatic phase of AD modified the behavior of microglia/macrophages. This prompted the formation of physical barriers around amyloid plaques, consequently inhibiting the development of dystrophic neurites at later stages and leading to substantial cognitive improvements in AD mice (Jović et al., 2019).

Animal studies have elucidated mainly the effects of n-3 PUFAs on Aβ, and several potential mechanisms underpinning their impact on Aβ have been proposed. Primarily, n-3 PUFAs, particularly DHA, have been found to diminish the production of toxic Aβ. Research by Lim et al. indicated that DHA modulates the lateral mobility of APP and the three APP secretases (α, β, and γ), consequently reducing β-C-terminal fragment (βCTF) production. This effect is achieved by lowering the activity of β- and γ-secretases, further curbing the formation of Aβ. Concurrently, DHA enhances non-amyloidogenic processing by increasing the stability of α-secretase. Furthermore, DHA suppresses the activity of HMG-CoA reductase, decreasing cholesterol production and facilitating its transfer from RAFT to non-RAFT domains. These changes are associated with reduced γ-secretase activity and presenilin-1 protein levels, thereby downregulating Aβ production (Fig. 2A) (Lim et al., 2005). Additionally, DHA contributes to the decline in Aβ by elevating LR11 levels in the membrane fractions of the mouse brain, consequently reducing the transportation of APP to Aβ-producing secretase (Ma et al., 2007). Collectively, these findings suggest that DHA effectively shifts APP from amyloidogenic pathways to non-amyloidogenic pathways, thereby effectively reducing the release of Aβ (Grimm et al., 2011).

N-3 PUFAs, in another potential mechanism, have been shown to enhance the degradation of Aβ (Saido and Leissring, 2012) (Fig. 2B). A study by Grimm et al. illustrated that EPA, a type of n-3 PUFA, directly amplifies the activity of the insulin-degrading enzyme (IDE), as well as its gene expression, thereby bolstering the degradation of Aβ. Furthermore, DHA has been shown to increase the release of IDE from exosomes, modifying IDE sorting and promoting Aβ degradation in the extracellular environment (Farris et al., 2003; Grimm et al., 2016). Additionally, n-3 PUFAs have been found capable of inhibiting or even reversing the formation of Aβ oligomers, thereby mitigating Aβ-associated neurotoxicity (Florent et al., 2006; Hashimoto et al., 2009; Hossain

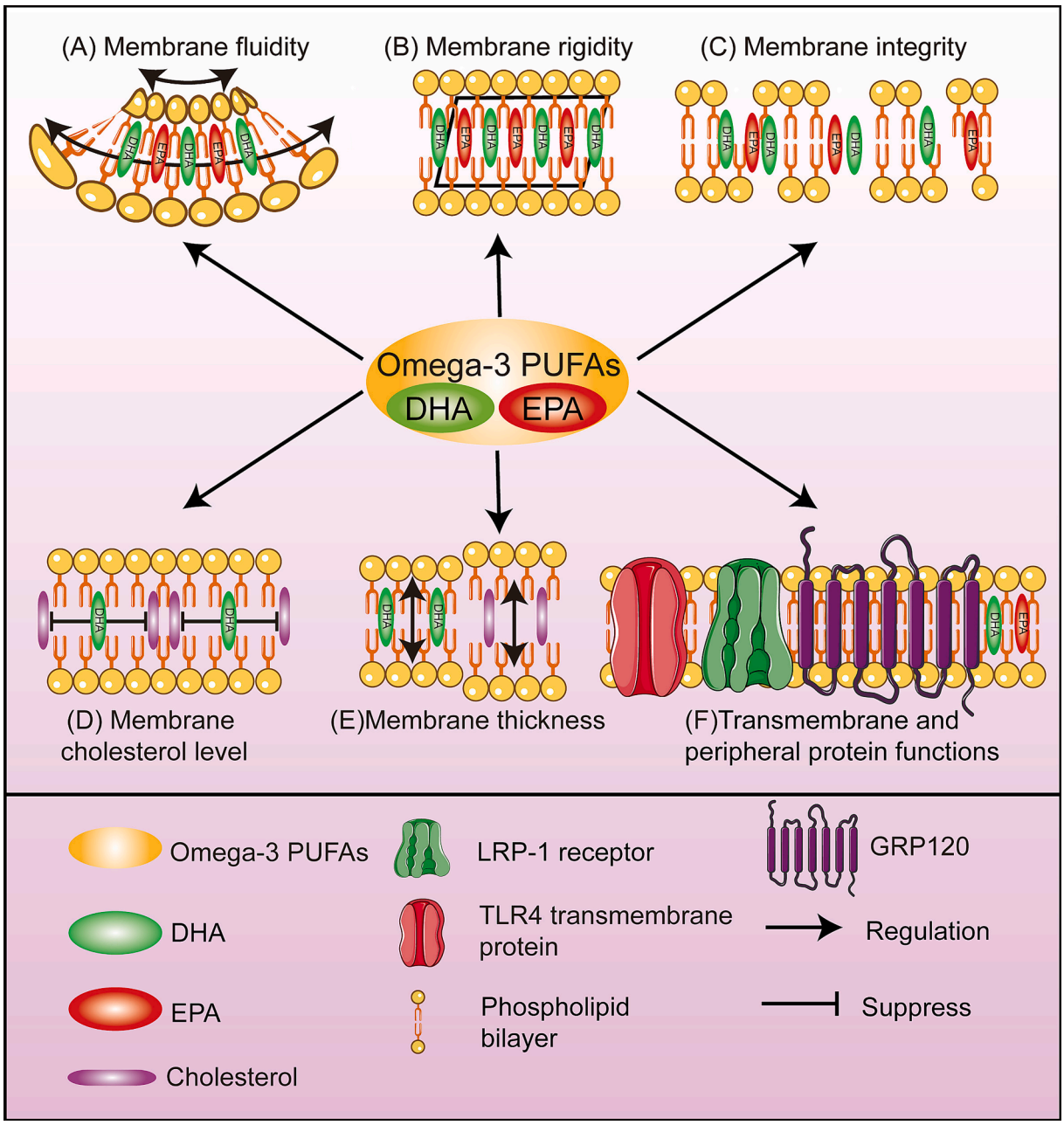

Fig. 1. Membrane regulatory functions of n-3 PUFAs in AD. (A) Enrichment of n-3 PUFAs, including DHA and EPA, in membrane glycerophospholipids (GPL) regulates membrane fluidity. Highly fluid membranes can enhance membrane dynamics to facilitate processes such as lateral diffusion of membrane proteins. (B) Enrichment of PUFAs, including DHA and EPA, in membrane GPL, enhances age-related membrane rigidity. Highly deformable DHA-rich membranes also support rapid conformational changes of membrane proteins. (C) N-3 PUFAs, including DHA and EPA, may protect BBB integrity in AD. (D) DHA had a greater total and HDL cholesterol-raising effect, resulting in a lower cholesterol/HDL ratio. (E) Lipid bilayers composed of DHA-containing GPLs are thinner than those composed of desaturated PLs and cholesterol. Loosely packed thin membranes may have increased permeability to ions and small molecules. (F) N-3 PUFAs improve neuronal membrane permeability and regulate transmembrane and peripheral protein functions, including receptors, enzymes, ion channels, production and activity of neurotransmitters, and signal transduction.

et al., 2009; Teng et al., 2015). It is noteworthy that both *in-vitro* and *in-vivo* studies have highlighted that compared to ApoE2 and ApoE3, ApoE4 not only promotes the seeding of Aβ peptide into oligomers, protofibrils, and fibrils (Hashimoto et al., 2012; Hori et al., 2015; Liu et al., 2017) but also hinders the enzymatic degradation of Aβ (Deane et al., 2008) and its clearance from the brain (Castellano et al., 2011).

Lastly, n-3 PUFAs have been found to expedite the clearance of Aβ (Fig. 2C). Various pathways contribute to the expulsion of Aβ from the brain, including autophagy-mediated protein clearance (Barbero-Camps et al., 2018), immune cell-mediated uptake (Bao et al., 2016; Koistinaho et al., 2004), clearance through the glymphatic system (Ren et al., 2017), and transport across the BBB (Kanekiyo et al., 2013; Storck et al., 2018). N-3 PUFAs have been demonstrated to accelerate Aβ clearance through multiple pathways (Fig. 2C).

Supplementation with n-3 PUFAs and Resveratrol enhanced macrophage phagocytosis of Aβ, thereby affecting brain amyloidosis (Famenini et al., 2017). Concurrently, other studies have recorded the stimulatory effect of n-3 PUFAs on microglial Aβ42 phagocytosis and interstitial Aβ clearance (Hjorth et al., 2013; Ren et al., 2017). Moreover, FO supplementation was found to increase the brain content of the Aβ

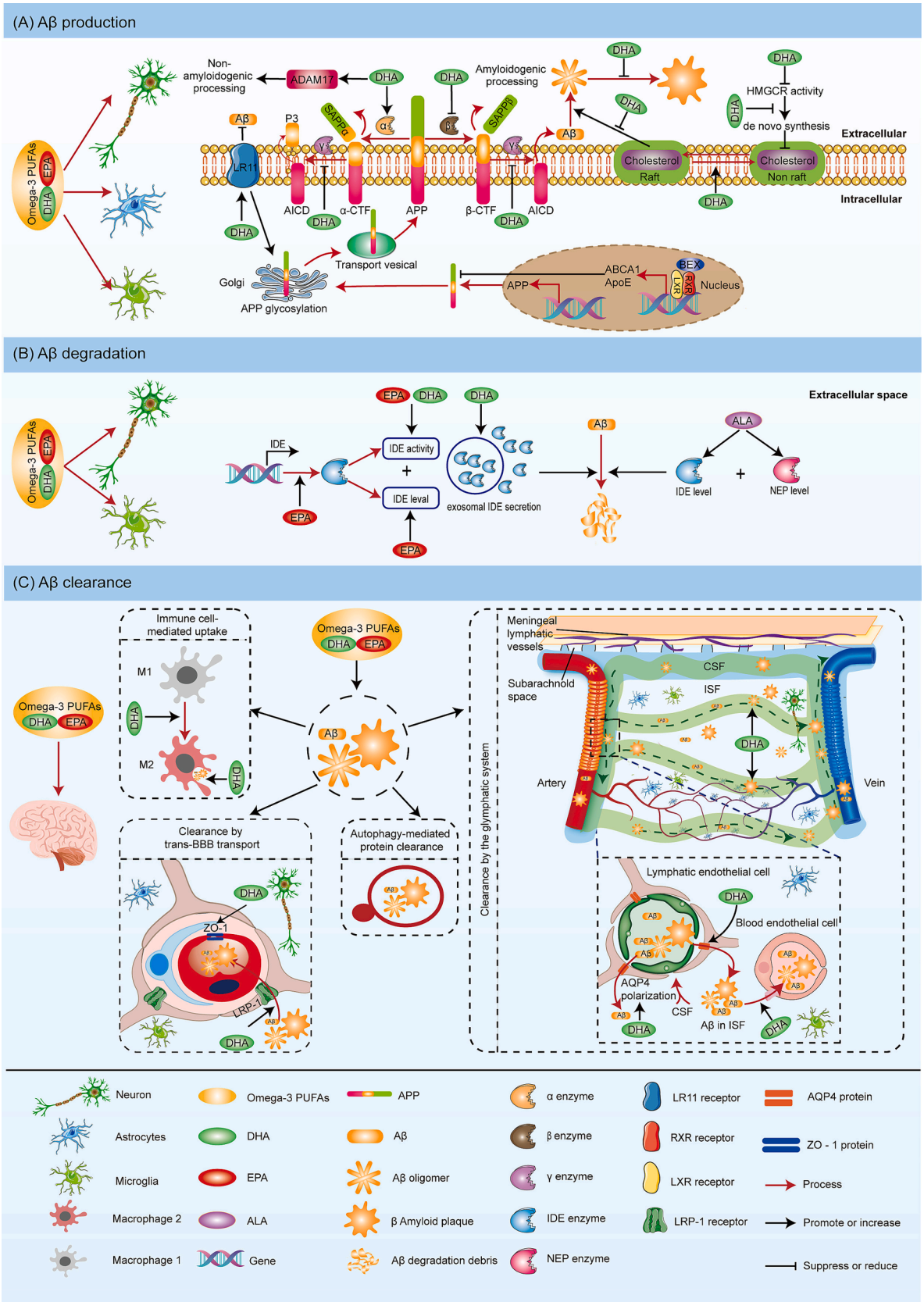

Fig. 2. Brain clearance functions of n-3 PUFAs in AD. (A) N-3 PUFAs may decrease Aβ production by increasing non-amyloidogenic processing and decreasing amyloidogenic processing. (B) N-3 PUFAs, including EPA, DHA and ALA, increase Aβ-degradation by affecting insulin-degrading enzyme (IDE) and neprilysin (NEP). (C) N-3 PUFAs accelerate Aβ clearance from the brain by multiple clearance pathways, such as autophagy-mediated clearance of the protein, immune cell-mediated uptake, lymphatic system clearance, and transport across the BBB.

transporter protein transthyretin (TTR) in elderly rats, thereby speeding up Aβ clearance (Puskás et al., 2003), a finding which was later confirmed in a clinical study involving 174 CE patients (Faxén-Irving et al., 2013).

Furthermore, DHA has been recognized as an agonist of several nuclear receptors. Its combination with Bexarotene, an agonist of the nuclear receptors LXR:RXR and PPAR:RXR, resulted in diminished amyloid accumulation in AD mouse models, cognitive improvement, and offset adverse effects of a single administration (Casali et al., 2015). Recent research has pointed to the critical role of the paravascular pathway network of the lymphatic system in efficiently removing extracellular solutes (including Aβ) from the brain (Iliff et al., 2012). Our study was the first to demonstrate that medications could influence the activity of the brain clearance system, with n-3 PUFAs beneficially impacting AD mice by activating the AQP4-mediated glymphatic pathway to remove Aβ in the brain (Ren et al., 2017). Moreover, beyond brain clearance, enhancing Aβ transport from the brain to blood offers another significant clearance pathway. Our research indicated that supplementation with n-3 PUFAs-rich FO significantly increased the expression of LRP-1, the primary efflux transporter of BBB, subsequently facilitating the clearance of Aβ from the brain to the circulation.

8. N-3 PUFAs and neuroinflammation modulation

Neuroinflammation plays a pivotal role in the progression of AD. The activation of microglia and astrocytes, in addition to their direct neurotoxic impacts, exacerbates the accumulation of Aβ, expediting the disease's progression (Akiyama et al., 2000). Human clinical trials have yielded inconsistent results. In the 2009 OmegAD study, dietary supplementation with n-3 PUFAs in 35 patients with mild to moderate AD for six months had no impact on markers of inflammation in the CSF and plasma (Freund-Levi et al., 2009). Simultaneously, a randomized controlled trial (RCT) conducted with 33 patients diagnosed with AD who received daily n-3 PUFAs treatment for six months showed that CSF biomarkers [Aβ 38, Aβ 40, Aβ 42, t-tau, p-tau, acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), soluble IL-1 receptor type II (sIL-1RII), and IL-6] remained consistent, with a significant increase in chitinase-3-like protein 1 (YKL-40) and neurofilament light (NFL), indicating a rise in inflammation and axonal injury (Tofiq et al., 2021).

Deficiency in n-3 PUFAs has been associated with heightened systemic inflammatory markers in adult female rats (Morgese et al., 2020), while bioactive lipid mediators (oxylipins) exhibiting anti-inflammatory and pro-catabolic properties have been shown to mitigate and resolve inflammation (Fig. 3A). N-3 PUFAs have been reported to stimulate G-protein coupled receptor 120 (GPR120) receptors to inhibit Toll-Like Receptor 4 (TLR4) and related inflammatory responses triggered by Nuclear factor kappa B (NF-Kb) (Fig. 3B) (Oh et al., 2010). Notably, n-3 PUFAs can manifest anti-inflammatory attributes by competing with n-6 PUFA and replacing ARA in membrane PLs, thereby curtailing the production of proinflammatory ARA (Fig. 3D) (Simonetto et al., 2019). Concurrently, n-3 PUFAs exhibit neuroinflammatory inhibition by mitigating amyloid load and tau hyperphosphorylation (Breitner et al., 2011; Vom Berg et al., 2012). Both EPA and DHA significantly contribute to this anti-inflammatory mechanism. EPA is a precursor to eicosanoids, including the 3-series prostaglandins and thromboxanes, the 5-series leukotrienes, and (alongside DHA) anti-inflammatory resolvins and neuroprotectins that are less potently inflammatory (Wood et al., 2022). EPA can also vie with ARA for the COX and 5-Lipoxygenase (5-LOX) enzymes (Zulyniak et al., 2016), thereby reducing ARA metabolism and lowering the level of ARA-derived inflammatory mediators (Bagga et al., 2003; Zulyniak et al., 2013) (Fig. 3C). DHA competes with ARA for incorporation into cell membranes, thus mitigating brain inflammation. This observation was corroborated by Calon et al., who found a significant decrease in DHA levels in the frontal cortex of aged transgenic mice on a restricted diet of n-3 PUFAs at 17 months. Additionally, DHA supplementation significantly diminished ARA levels and ameliorated inflammatory responses (Calon et al., 2004).

Moreover, DHA generates oxygenated derivatives known as docosanoids. These substances, in conjunction with active retinoid X receptors (RXR), actuate the peroxisome proliferator-activated receptor (PPAR), a regulatory entity governing inflammation and cell survival (Heras-Sandoval et al., 2016). Hopperton et al. observed that dietary intake of FO led to a marked diminution in the expression of neuroinflammatory genes in a murine AD model (Hopperton et al., 2018). Additionally, FO consumption appears to alleviate systemic inflammation and ameliorate depressive symptoms induced by inflammation, effectuated by alterations in energy, tryptophan, and nicotinic acid metabolism (Peng et al., 2020). In a recent investigation, it was unequivocally established that derivatives of lipoxygenase (LOX) – specifically 5-hydroxyeicosapentaenoic acid (HEPE) and 4-hydroxydocosahexaenoic acid (HDHA) – in conjunction with cytochrome P450 (CYP450)-produced metabolites such as 18-HEPE, 20-HDHA, 17(18)-epoxyeicosatetraenoic acid (EpETE), and 19(20)-epoxydocosapentaenoic acid (EpDPA), serve as pivotal agents in the antidepressant, anti-inflammatory, and neuroprotective capacities manifested by EPA and DHA (Borsini et al., 2021). On a molecular dimension, there exists compelling evidence to suggest that both EPA and DHA exert a significant influence on immune response mechanisms and oxidative stress pathways, including, but not limited to, those orchestrated via Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2), Signal transducer and activator of transcription 3 (STAT3), Interferon (IFN), and IL-1 signaling cascades. Furthermore, DHA distinctly modulates cell proliferative processes and neural developmental pathways, chiefly through the mechanistic involvement in cAMP-response element-binding protein (CREB) signaling pathways (Borsini et al., 2020). This differential regulation elucidates the comprehensive role that these compounds play in fostering neural health and resilience, paving the way for future explorations in the domain of neurological well-being.

Numerous studies underscore the potent anti-inflammatory effects of n-3 PUFAs in murine models of AD. Investigations reveal that the inherent expression of n-3 PUFAs in APP/fat-1 mice mitigates the inflammatory response, thereby ameliorating cognitive deficits and apathy-like symptoms associated with AD, compared to their APP littermates (Park et al., 2020; Wu et al., 2016). In concordance with these findings, our research detected a significant reduction in glial activation and NF-κB expression in both APP/PS1 mice and Aβ-injected fat-1 mice following n-3 PUFA supplementation (Ren et al., 2017; Xie et al., 2020; Yan et al., 2020). Contrastingly, Jović et al. proposed that transient FO treatment during the asymptomatic phase of AD could modulate the activity of microglia/macrophages, prompting them to form a physical barricade around amyloid plaques, effectively suppressing the emergence of dystrophic neurites (DNs) by reducing Aβ levels and tau hyperphosphorylation (Jović et al., 2019). Moreover, evidence suggests that in animal models of AD, other n-3 PUFAs-derived components such as ALA (Ali et al., 2020) and EPA (Vors et al., 2017), or the combination of n-3 PUFAs with other nutrients such as Co-Q10 (Ibrahim Fouad, 2020) could also attenuate neuroinflammation and ameliorate the disease phenotype of AD mice.

9. The role of N-3 PUFAs in cognitive function

Several studies have established a substantial link between n-3 PUFAs and cognitive function. Clinical trials have produced inconsistent outcomes. Current randomized clinical trials (RCTs) examining the role of n-3 PUFAs in AD include single interventions using DHA, EPA, and FO, alongside multi-domain lifestyle interventions such as physical activity (PA), cognitive training, nutritional advice, and combined interventions with other nutrients. The effectiveness of a single intervention varies across different populations and treatment durations. The OmegaAD Study, a pivotal randomized trial, examined the impact of n-3 PUFAs on cognitive performance in AD patients over 12 months. The Mini-Mental State Examination (MMSE) and the cognitive

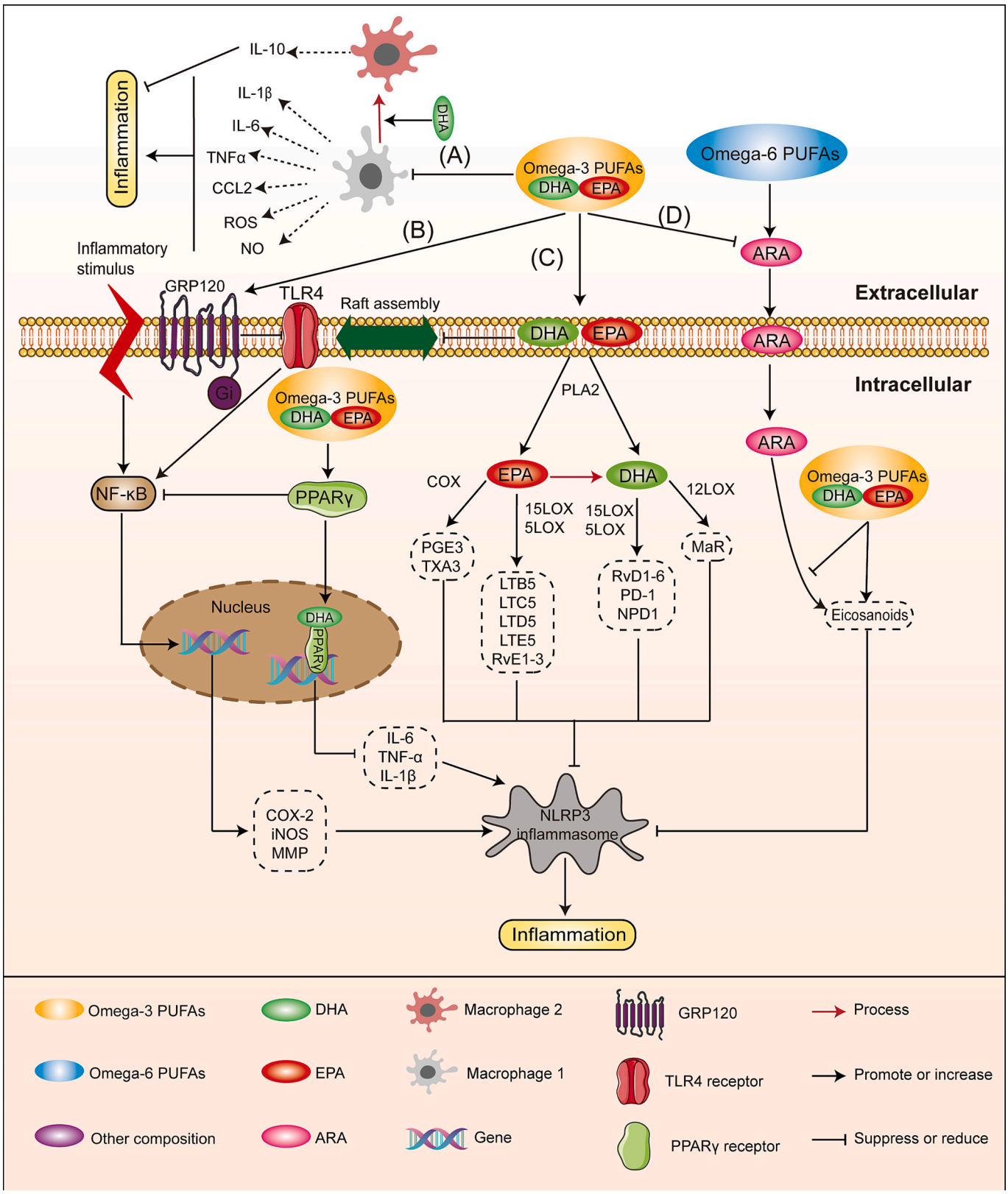

Fig. 3. The anti-inflammatory function of n-3 PUFAs in AD. (A) N-3 PUFAs may affect the activity of macrophages, decreasing the content of active inflammatory factors and inhibiting the inflammatory response. (B) N-3 PUFAs affect the behavior of GRP120 membrane protein and PPAR nuclear activin protein, leading to a decrease in the activation of pro-inflammatory transcription factors, such as NF-κB, thereby reducing many cytokines, chemokines, adhesion molecules, inflammatory enzymes and protease gene expression to play an anti-inflammatory effect. (C) The two most important n-3 PUFAs, DHA and EPA, can be utilized for enzymatic conversion by LOX and COX enzymes that generate bioactive, anti-inflammatory downstream metabolites. (D) N-3 PUFAs can exhibit anti-inflammatory characteristics by contending with n-6 PUFA and substituting ARA in membrane phospholipids, decreasing the generation of proinflammatory ARA.

component of the Alzheimer's Disease Assessment Scale (ADAS-cog) were utilized to evaluate treatment efficacy. However, n-3 PUFAs only significantly reduced cognitive decline in a subset of 32 patients with very mild AD (MMSE > 27) (Eriksdotter et al., 2015).

In trials where diagnoses ranged from mild to moderate severity or amnesiac MCI, no significant difference was observed in the changes in cognitive components among patients with moderately severe MCI. Participants with MCI did, however, display substantial improvements in ADAS-cog in the n-3 PUFAs group (Chiu et al., 2008). Additionally, n-3 PUFA supplementation in patients with mild-to-moderate AD did not slow the progression of cognitive decline (Freund-Levi et al., 2006), nor did it affect neuropsychiatric symptoms (Freund-Levi et al., 2008). Nevertheless, positive effects were observed in a small subset of very mild AD patients regarding MMSE scores (Freund-Levi et al., 2006) and psychiatric symptoms in non-ApoE4 carriers (Freund-Levi et al., 2008), as well as in their weight and appetite (Irving et al., 2009).

While many clinical studies report limited cognitive protective effects from n-3 PUFA supplementation in individuals with cognitive impairments and dementia (Phillips et al., 2015; Quinn et al., 2010), certain studies have revealed its benefits. N-3 PUFA supplementation has also been observed to enhance memory function in healthy older adults without dementia (Külzow et al., 2016), though no impact on inherent capacity was noted (Giudici et al., 2020). In a Taiwanese placebo-controlled trial, patients with MCI or AD, supplemented with either DHA, EPA, or a combination, experienced no cognitive decline but showed improvements in speech capability and constructional praxis subitems of ADAS-cog (Lin et al., 2022a). Furthermore, daily DHA supplementation (2 g/day) for a year significantly improved cognitive function and reduced the progression of hippocampal atrophy in patients with MCI (Zhang et al., 2017).

DHA supplementation has been widely researched for its potential benefits on MCI, with results indicating improvements in associative learning and both immediate and delayed verbal recognition memory (Lee et al., 2013; Phillips et al., 2015). However, a study comparing non-ApoE4 carriers and ApoE4 carriers revealed that while DHA supplementation led to a three-fold increase in CSF EPA levels in non-ApoE4 carriers, there was no discernible impact on brain volume or cognitive scores in either group (Arellanes et al., 2020). The Multidomain Alzheimer Preventive Trial (MAPT), which aimed to examine the effects of n-3 PUFA supplementation and a multidomain intervention (incorporating physical activity, cognitive training, and nutritional advice), found no significant reduction in cognitive decline among older individuals with memory complaints, regardless of whether the interventions were used alone or in combination years (Andrieu et al., 2017). Moreover, secondary analyses of MAPT indicated that n-3 PUFA supplementation did not enhance muscle strength (Rolland et al., 2019) or intrinsic capacity (Giudici et al., 2020). Nonetheless, physical activity levels differed significantly between the placebo/usual care and n-3/usual care groups at 2- and 3-year follow-ups (Barreto et al., 2018). A large-scale lifestyle intervention trial among community-dwelling seniors (n = 1588) with memory impairments demonstrated that long-term lifestyle interventions and n-3 PUFAs treatment did not reduce frailty or morbidity.

The Souvenaid trial underscored the potential benefits of supplementing n-3 PUFAs with other nutrients. Compared to single interventions or multidomain AD prevention approaches, the combination of n-3 PUFAs and other nutrients showed more promising clinical results. In a study involving 39 AD patients over a 12-month treatment period, the combined supplementation of n-3 PUFAs and alpha-lipoic acid decelerated the decline of instrumental activities of daily living (IADL) scores and significantly influenced the MMSE scores when compared with the placebo group (Shinto et al., 2014). N-3 PUFAs, when supplemented, can also enhance cognitive performance in moderate AD patients, potentially influenced by homocysteine (tHcy) levels, which relate to B vitamin status. The interplay between B vitamins and n-3 PUFAs has been reported to affect the rate of brain atrophy in patients with MCI (Malouf and Evans, 2008). Moreover, n-3 PUFA supplementation seems to improve cognitive performance and working memory in older adults, particularly when coupled with B vitamins (Jernerén et al., 2019), xanthophyll carotenoids (specifically lutein, zeaxanthin, and *meso*-zeaxanthin), and Vitamin E (d-α-tocopherol). Increasing the intake of carotenoids and n-3 PUFAs may help mitigate the risk of cognitive decline and dementia in later life stages (Power et al., 2022). However, it is important to note that the positive effects observed in cognitively healthy older adults' working memory may not be solely attributed to the influence of n-3 PUFAs.

N-3 PUFAs supplements are generally well-tolerated according to existing research. While n-3 PUFAs, particularly DHA, may not be a definitive treatment for cognitive issues or AD, their promise as an early intervention strategy for neuroprotection among individuals with MCI and in the healthy elderly population is noteworthy. The clinical heterogeneity of dementia necessitates further exploration. The potential for additional supplementation strategies and nutrient interactions to prevent or mitigate cognitive decline in older adults could be unveiled by examining the combined effects of n-3 PUFAs and other nutrients, such as α-lipoic acid and B vitamins. Furthermore, investigating the effects of different durations and doses across diverse populations could help discern the correlation between n-3 PUFAs and cognitive improvement in MCI. Notably, Wood et al. have proposed that a DHA supplementation duration of at least five months and a daily dose exceeding 900 mg are required to impact cognitive function in the elderly significantly (Wood et al., 2022). A recent frequentist-model based network *meta*-analysis of 52 RCTs involving 21,111 participants, it was found that an extended regimen of high-dose (1500–2000 mg/day) EPA-predominant n-3 PUFAs, supplemented with anti-oxidants, demonstrated the most pronounced potential for cognitive enhancement among all examined treatments (Tseng et al., 2023). A summary of research findings on n-3 PUFAs in clinical trials related to AD is provided in Supplementary Table 1.

Numerous preclinical investigations have substantiated the association between n-3 PUFAs intake and AD. A systematic review and *meta*-analysis conducted in 2012 demonstrated improved cognitive function in AD model mice treated with n-3 PUFAs, with effects appearing more pronounced in rats than mice and in males over females (Hooijmans et al., 2012). This benefit was echoed across a variety of AD rodent models, including aged transgenic mice (Calon et al., 2005; Calon et al., 2004; Lim et al., 2005; Ma et al., 2007), APP transgenic mice (Wu et al., 2016), double transgenic mice APP/PS1 (Arendash et al., 2007; Yan et al., 2020), 3xTg-AD transgenic mice (Lebbadi et al., 2011; Ma et al., 2009), 5xFAD transgenic mice (Casali et al., 2015; Fang et al., 2019; Milanovic et al., 2018; Park et al., 2020), and intracerebroventricular Aβ 1–40 model mice (Ali et al., 2020; Hopperton et al., 2016; Hopperton et al., 2018; Park et al., 2020; Ren et al., 2017). These studies collectively suggest that n-3 PUFAs may ameliorate cognitive impairment in AD, serving as a preventive or therapeutic measure. A summary of research findings relating to n-3 PUFAs in animal models of AD is provided in Supplementary Table 2.

Notably, the cognitive domains affected by n-3 PUFAs are central to the performance of daily activities and overall quality of life. It is also important to mention that individual response to n-3 PUFAs may vary, possibly due to genetic variability, baseline n-3 status, and specific health conditions. Therefore, personalized approaches could be beneficial in the future. Despite the need for further research, the existing evidence indicates that n-3 PUFAs hold considerable promise as a dietary intervention for enhancing cognitive health and potentially mitigating neurodegenerative disorders.

10. Age-Related shifts in N-3 PUFAs metabolism

The lipid profile of the brain exhibits a unique characteristic; approximately a third of the brain's lipid constituents are comprised of DHA and ARA, amounting to around 10,000 nmol/g, and EPA,

constituting about 250 nmol/g (Bazinet et al., 2020). To note, non-pathological aging led brain atrophy might influence fatty acid, possibly DHA composition, albeit findings on this are varied (Lacombe et al., 2018). Furthermore, the dietary intake and subsequent metabolism of these fatty acids can influence their effective reach to the brain. Studies show that the primary source of brain DHA is plasma non-esterified fatty acid (NEFA) and a daily brain DHA uptake is between 2.4 and 3.8 mg/brain, based on imaging studies involving labeled NEFA-DHA infusion in humans, that minimally undervalue the actual rate of brain DHA assimilation (Chen et al., 2015). Chen et al. (Chen et al., 2013) evaluated the brain's uptake dynamics of EPA employing a radiolabeled EPA in an *in vivo* infusion model (Rapoport et al., 2011), discerning that EPA levels in the brain are 250 to 300 times lower than DHA due to EPA's swift β-oxidation and limited preservation in brain phospholipids, an occurrence maintained by multiple concurrent processes.

In the evolving panorama of gerontological research, the modulation of n-3 PUFAs metabolism throughout the aging process (Mutlu et al., 2021) represents a burgeoning area of investigation, holding implications for the efficacious deployment of these pivotal nutrients in therapeutic interventions (Chappus-McCendie et al., 2019; Palmer and Jensen, 2022). Various studies have sought to delineate the intricate interplays between aging and shifts in the metabolic pathways associated with n-3 PUFAs (Ali et al., 2023; Joffre et al., 2020). In this regard, a meticulous appraisal of current literature facilitates a nuanced understanding of this dynamic, thereby elucidating potential avenues for tailored interventions in the aging demographic. Initiating this exploration is the acknowledgment of age-associated alterations in digestive efficiency (Rémond et al., 2015), which could potentially impede the optimal absorption and utilization of n-3 PUFAs. As delineated by several researchers, the aging process heralds a decrement in the enzymatic conversion of precursor fatty acids to bioactive forms (Das, 2018). This scenario necessitates an enhanced focus on the provision of readily available forms of these fatty acids to surmount potential metabolic impediments in the elderly. Furthermore, a compelling dimension to consider is the age-related alterations in cellular membrane composition and fluidity. DHA, an integral component of neuronal membranes, plays a crucial role in maintaining cognitive function and neuronal health. Aging, however, tends to disrupt the equilibrium in membrane lipid composition, potentially impacting the efficacy of DHA incorporation into phospholipids and, consequently, its neuroprotective capacities (Alvarez et al., 2001).

From a molecular perspective, n-3 PUFAs have been lauded for their modulatory influence on several signaling pathways, encompassing anti-inflammatory and antioxidative responses (Calder, 2015). Nevertheless, advancing age might evoke a diminished responsiveness of these pathways to n-3 PUFAs, a scenario that warrants meticulous investigation to delineate optimized intervention strategies that can transcend these age-related barriers. Concomitantly, the interaction between aging and the gut microbiome emerges as a pivotal consideration in the discourse on n-3 PUFAs metabolism. A growing body of evidence alludes to the role of gut microbiota in influencing the metabolism and bioavailability of these fatty acids, with potential modifications occurring with aging (Watson et al., 2018). Thus, a multi-dimensional approach that encapsulates an understanding of the symbiotic relationships between gut microbiota and n-3 PUFAs metabolism is essential to craft interventions with heightened efficacy in the aging populace. Thus, navigating the complex narrative of n-3 metabolism in the context of aging necessitates a deeply nuanced, evidence-based approach. The present discourse stands enriched by scholarly contributions, illuminating the multifactorial dynamics that characterize the shifting landscape of n-3 metabolism in aging individuals. As the scientific community strides forward, the incorporation of insights from recent research becomes instrumental in honing interventions that adeptly address the metabolic shifts accompanying aging, thereby enhancing the efficacy and precision of therapeutic strategies anchored on the salutary impacts of n-3 PUFAs.

11. Other protective effects of N-3 PUFAs

N-3 PUFAs, particularly DHA, are fundamental for neuronal function, signaling, and neuroprotection (Moriguchi et al., 2000; Salem et al., 2001b). The pivotal role of DHA in prenatal neurodevelopment is well-documented (Mita et al., 2016; Rogers et al., 2013). Recent investigations have highlighted the impact of n-3 PUFAs on neuronal energy metabolism. N-3 PUFAs have been found to enhance the expression of genes that encode energy-metabolizing enzymes, such as cytochrome oxidase, Nicotinamide adenine dinucleotide (NADH) dehydrogenase, and ATP synthase, in the rat brain (Kitajka et al., 2002; Ximenes da Silva et al., 2002). DHA has also demonstrated the ability to temper hyperoxia-induced surges in mitochondrial reactive oxygen species (ROS), preserve mitochondrial Ca^{2+} buffering capacity, and ameliorate mitochondrial dynamics both *in vitro* and *in vivo* (Chudoba et al., 2019; Mayurasakorn et al., 2016; Zhang et al., 2018). Recent studies have shown that FO restores age-related respiratory decline and enhances ATP production in the brain of aged mice (Afshordel et al., 2015) and elevates ATP-related oxygen consumption rate (OCR) under hypoglycemia or hyperglycemia. Consequently, n-3 PUFAs may slow the progression of dementia in some patients with late-onset AD (LOAD) (Lau et al., 2020).

Evidence suggests that n-3 PUFAs, particularly DHA and EPA, play crucial roles in brain health and function. Their potential neuroprotective actions provide a promising avenue for preventing or treating neurodegenerative diseases, including dementia and AD. However, further research is needed to fully understand the complex mechanisms involved and translate these findings into effective therapeutic strategies.

12. Challenges and controversies

Although many studies support the beneficial impact of n-3 PUFAs on AD and dementia, conflicting outcomes have been reported. Some trials have failed to observe significant cognitive improvements following n-3 PUFA supplementation, leading to ongoing debates in the field (Burckhardt et al., 2016). For example, the Cochrane Review in 2012, an extensive analysis of RCTs, concluded that n-3 PUFA supplementation did not slow cognitive decline in patients with mild to moderate AD (Sydenham et al., 2012). The discrepancies in study outcomes could be attributed to multiple factors, such as differences in study design, participant characteristics (including the severity of cognitive impairment and genetic makeup), the type, dosage, and duration of n-3 PUFA supplementation, and the specific cognitive outcomes assessed (Andrieu et al., 2017).

Further determining the optimal dosage and duration of n-3 PUFA supplementation is a significant challenge. Doses used in studies vary widely, and the most effective dose for cognitive health has yet to be determined. Moreover, the ideal duration of supplementation is still unclear. Some studies suggest long-term supplementation is needed for significant cognitive benefits, while others show effects with shorter durations (Jiao et al., 2014). Additionally, individual factors such as age, sex, baseline n-3 status, and genetic variants may influence the body's response to supplementation (Luchtman and Song, 2013). More research is needed to tailor n-3 PUFA supplementation strategies to individual needs and characteristics. More importantly, the effects of n-3 PUFAs on cognitive health may also be influenced by the interplay with other nutrients and lifestyle factors. For instance, a higher n-6 to n-3 ratio, common in Western diets, may negate the beneficial effects of n-3 PUFAs (Simopoulos, 2016).

Moreover, lifestyle factors such as physical activity and cognitive engagement may interact with n-3 PUFAs effects. For instance, the glymphatic system, a brain-wide network of perivascular spaces responsible for waste clearance, is influenced by sleep patterns and

possibly modulated by n-3 PUFAs (Iliff et al., 2012). Regular physical activity has been shown to enhance the benefits of n-3 PUFAs on brain health (Su, 2010). Cognitive engagement, such as intellectually stimulating activities, could also enhance the cognitive benefits of n-3 PUFAs (Fratiglioni et al., 2004). In light of these challenges, a more holistic approach, incorporating diet, lifestyle, and genetic factors, will likely be necessary to fully understand and harness the potential of n-3 PUFAs in promoting cognitive health. Furthermore, future research should aim to reconcile conflicting outcomes, determine optimal dosage and supplementation duration, and better understand the intricate interplay between n-3 PUFAs, other nutrients, and lifestyle factors. Despite the challenges, the potential of n-3 PUFAs in the battle against AD and dementia remains significant, providing a compelling direction for future investigations.

In the vibrant and rapidly evolving field of biomedical research, the potential application of n-3 PUFAs as either a standalone treatment or an adjunct therapy in the context of aging-related pathologies warrants meticulous scrutiny. As an integral nexus in the complex web of nutritional neuroscience, the elucidation of the nuanced roles of n-3 PUFAs in both preventative and curative paradigms is imperative. Commencing with the preventative sphere, the propensity of n-3 PUFAs to forestall the onset of microvascular and glymphatic dysfunction presents a significant area of interest. Emerging literature has begun to delineate the potent anti-inflammatory and antioxidant properties of these fatty acids, which are believed to be instrumental in mitigating the deleterious alterations often observed in microvascular networks as aging progresses. Moreover, the glymphatic system, a pivotal player in cerebral health, appears to be particularly receptive to the modulatory influences of n-3 fatty acids. The underlying mechanisms are hypothesized to involve the enhancement of clearance pathways for metabolic waste products, a process intrinsically tied to the prevention of neurodegenerative conditions. In contrast, the curative domain entails a more intricate examination of the restorative capabilities of n-3 PUFAs in reversing existing pathologies associated with aging. While optimism abounds regarding the ability of these fatty acids to modulate signaling pathways, promote neuroplasticity, and foster vascular health, the existing body of research still stands at a relatively nascent stage. Consequently, proposing n-3 PUFAs as a sole treatment avenue may be somewhat premature, necessitating further expansive and rigorously conducted studies to substantiate such a stance.

Transitioning to the dialogue on whether n-3 PUFAs should be envisaged as an adjunctive therapy, one cannot overlook the symbiotic potential that this approach holds. In concert with established therapeutic regimens such as antioxidants, the integration of n-3 PUFAs could potentially amplify the beneficial neuroprotective outcomes (Tong et al., 2020), fostering a more harmonized approach to tackling aging-related pathologies. Notably, the collaborative effect witnessed in tandem with other nutrients or pharmaceutical agents might augment the protective barriers against microvascular and glymphatic dysfunction, orchestrating a more synergized and potent defensive front. Furthermore, the evaluation of the therapeutic efficacy of n-3 PUFAs necessitates a multidimensional approach, encompassing a consideration of dosage optimization, duration of intervention, and individual responsiveness, which might vary significantly based on genetic predispositions and existing health statuses.

As we navigate the complex terrain of aging-related pathologies, the dynamic role of n-3 PUFAs beckons a deeper exploration. While their preventative prowess seems more pronounced, especially in the realm of microvascular and glymphatic health, the curative potential cannot be relegated to the periphery. A balanced approach, wherein n-3 PUFAs are leveraged as both a preventive and a supplementary curative agent, might herald a new epoch in the management of aging-related ailments AD and dementia, thus fostering a holistic approach to healthcare, firmly grounded in evidence-based science and innovative thinking.

13. Future perspectives and research opportunities

As our understanding of the effects of n-3 PUFAs on AD and dementia evolves, one promising avenue of research is personalized supplementation approaches. Given individuals' genetic and metabolic diversity, n-3 PUFA supplementation may not have a uniform effect across the population (Luchtman and Song, 2013). For instance, the ApoE4 genotype, a significant genetic risk factor for AD, may affect n-3 PUFA metabolism and, thereby, the effectiveness of supplementation (Plourde et al., 2007). Future research should identify specific genetic and metabolic factors influencing an individual's response to n-3 PUFA supplementation. This could enable the development of personalized supplementation strategies tailored to an individual's unique needs and characteristics to optimize cognitive health benefits.

N-3 PUFAs are likely to have synergistic effects with other nutrients and therapies. For example, antioxidants such as vitamin E and astaxanthin could potentially enhance the neuroprotective effects of n-3 PUFAs (Barros et al., 2014; Huang et al., 2019). There is also interest in their potential synergy with glymphatic system modulation. Similarly, combining n-3 PUFAs with other therapies, such as physical exercise, cognitive training, and medications, might yield more significant cognitive benefits (Bo et al., 2019; Farioli Vecchioli et al., 2018). More research is needed to identify the most effective combinations of n-3 PUFAs with other nutrients and therapies and to determine the optimal dosages and timings for these combinations. In addition to natural n-3 PUFAs, research is exploring novel derivatives and formulations with enhanced efficacy and bioavailability. For example, n-3 fatty acid ethyl esters have been shown to have higher bioavailability compared to natural n-3 PUFAs (Offman et al., 2013). Similarly, research is investigating novel delivery systems for n-3 PUFAs, such as liposomes and nanoparticles, that could potentially improve their absorption and delivery to the brain (Dyall, 2015).

In the future, advancements in genomics, metabolomics, and other omics technologies could further enhance our ability to develop personalized n-3 PUFA supplementation strategies. Likewise, novel n-3 PUFA derivatives and formulations are promising to enhance the efficacy and bioavailability of these important nutrients. By continuing to investigate these and other opportunities, we can hopefully enhance our ability to harness the power of n-3 PUFAs to prevent and treat AD and dementia. As we move forward, we must continue to conduct rigorous, high-quality research to ensure that our understanding of the benefits of n-3 PUFAs is based on solid scientific evidence.

14. Conclusion

There is consistent evidence supporting the neuroprotective properties of n-3 PUFAs, with numerous epidemiological and interventional studies revealing their beneficial effects on cognitive health. However, the results of clinical trials have been mixed, with some showing significant cognitive benefits in early stage of AD and MCI. In addition to the anti-inflammatory and antioxidant properties and ability to support neuronal function and plasticity the potential of n-3 PUFAs in supporting glymphatic function and microvascular protection further strengthens the case for their inclusion in comprehensive management strategies. Furthermore, given their general safety and beneficial effects on overall health, n-3 PUFAs can be considered a valuable addition to existing treatment regimens for AD and dementia.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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