Review

Omega 3 fatty acids and neurodegenerative diseases: new evidence in clinical trials

Rossella Avallone [1]*, Giovanni Vitale [1] and Marco Bertolotti [2]

[1] Department of Life Sciences, Modena and Reggio Emilia University, 41125 Modena, Italy; rossella.avallone@unimore.it (R.A.); giovanni.vitale@unimore.it (G.V.)
[2] Division of Geriatric Medicine, Department of Biomedical, Metabolic and Neural Sciences, and Center for Gerontological Evaluation and Research, Modena and Reggio Emilia University, 41126 Modena, Italy; marco.bertolotti@unimore.it (M.B.)
* Correspondence: rossella.avallone@unimore.it; Tel.: +39-059-2055720 (R.A.)

Abstract: A nutritional approach could be a promising strategy to prevent or slow the progression of neurodegenerative diseases such as Parkinson's and Alzheimer's disease, since there is no effective therapy for these diseases so far. The beneficial effects of omega-3 fatty acids are now well established by a plethora of studies through their involvement in multiple biochemical functions, including synthesis of antinflammatory mediators, cell membrane fluidity, intracellular signalling and gene expression.
This systematic review will consider epidemiological studies and clinical trials that assessed the impact of supplementation or dietary intake of omega-3 polyunsaturated fatty acids on neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. Indeed, treatment with omega-3 fatty acids, being safe and well tolerated, represent a valuable and biologically plausible tool in the management of neurodegenerative diseases in their early stages.

Keywords: omega-3 polyunsaturated fatty acids; Parkinson's disease; Alzheimer's disease; clinical trials

1. Introduction

Several cerebral functions are determined by some nutrients, such as omega-3 polyunsaturated fatty acids (PUFAs), which are key membrane components involved in the proper neuronal functions through a range of potential mechanisms including increase of new synapse formation [1], effects on synaptic function, integrity and neurochemistry, and synaptic plasticity [2–5]. On the whole, this contributes to neuroplasticity, which it is associated with the enhancement of cognitive activity [6].
There is accumulating scientific evidence on the possible efficacy of PUFAs supplementation in neurodegenerative disorders [7,8], such as Parkinson's (PD) and Alzheimer's disease (AD) [9–13]. Although dietary recommendations are far from being a treatment for PD or AD, they may be able to alleviate some of the symptoms or slow the cognitive and physical decline.
The present study systematically reviews the effects of omega-3 polyunsaturated fatty acids' supplementation on cognitive function in patients with Parkinson's or Alzheimer's disease.
The main classes of PUFAs belong to the omega-3 one, which comprises α-linolenic acid (ALA, 18:3 ω-3), eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3) and to the omega-6 one, which comprises linoleic acid (LA, 18:2 ω-6) and arachidonic acid (ARA, 20:4 ω-6) [14]. DHA and ARA are the most important PUFAs in the brain [15]; in particular, DHA constitutes over 90% of the ω-3 PUFAs and 10%–20% of total lipids in the brain [16]. It is mainly incorporated in phosphatidylethanolamine, phosphatidylserine and in smaller amounts in phosphatidylcholine [17] at synaptic terminals, mitochondria and endoplasmic reticula. Indeed, DHA in able to modulate cellular characteristics and physiological processes including membrane fluidity, lipid raft function, neurotransmitter release, transmembrane receptor function, gene expression, signal transduction, myelination, neuroinflammation, neuronal differentiation and growth [18,19].
DHA results from ALA, while ARA from LA by desaturation and elongation of the carbon chain [20] (Figure 1). Humans can synthesize saturated and monounsaturated fatty acids (MUFAs), but they are not able to

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

synthesize ALA and LA due to the deficiency of the conversion enzyme ω-3-desaturase [21]. LA and ALA request the same conversion enzymes, consequently there is competitive inhibition between the two substrates. Delta-6-desaturase promotes the conversion of omega-3 fatty acids into omega-6 fatty acids; however an increased LA intake may shift the balance towards the conversion of omega-6 PUFA thus inhibiting the conversion of ALA to DHA [22].

Esterified DHA in food, is released by the intestinal lipases in free nonesterified form (DHA-FFA) in the small intestine and, after intestinal and hepatic metabolism, it can be found esterified in triglycerides and in phosphotidylcholine or as DHA-FFA bound to low density lipoprotein and albumin [23]. These various forms are dissociated at the blood-brain barrier (BBB) level through both active and passive processes which are mediated by endothelial lipases, fatty acid binding proteins (FABPs), and apolipoprotein E (ApoE) [24–27], whereas unesterified DHA easly passes the BBB [28]. Within the central nervous system, DHA is transported primarily via FABPs [25,26] and ApoE produced by astrocytes [27]. DHA is incorporated into membrane phospholipids mainly in the stereospecifically numbered-2 position through the action of coenzyme A [29]. However, through hydrolysis reactions catalysed by phospholipase, DHA can be released from membrane phospholipids. Both synthesis and hydrolysis represent mechanisms aimed at responding to dynamic cellular events and challenges during development and aging [14].

DHA, EPA and ARA are also important for the production of eicosanoids (prostaglandins, thromboxanes, leukotrienes) and, therefore, for their involvement in inflammation [20]. Metabolism of most eicosanoids implies the release of fatty acids esterified into phospholipids, by phospholipase A2 enzymes (PLA2). Consequently, increased levels of free fatty acids and lipid mediator biosynthesis take place particularly after inflammatory cell activation. The most frequently involved PLA2s in the cellular production of bioactive lipids are: the cytosolic calcium-dependent PLA2 (cPLA2), the cytosolic calcium-independent PLA2 (iPLA2) and the secretory PLA2 (sPLA2) [30]. Among them, cPLA2, shows a substrate specificity for phospholipids containing AA. cPLA2, however, can also hydrolyze phospholipids containing EPA, but the low abundance of this fatty acid allows cPLA2 to release AA in specific conditions [31]. Prostaglandins, leukotrienes and thromboxanes regulate inflammatory modulation and they are metabolized by cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) [32]. ARA is the precursor for the 2-series of prostaglandins and thromboxanes and the 4-series of leukotrienes. EPA is a precursor for the 3-series of prostaglandins and thromboxanes and the 5-series of leukotrienes [22]. As a result, ARA shows typical proinflammatory properties opposed to EPA that, in particular, produces anti-inflammatory effects [22]. Furthermore, 5-LOX is responsible for the generation of anti-inflammatory eicosanoids such as the D-series resolvins, protectins and maresins, which are derived from DHA and the E-series resolvins from EPA [33,34] (Figure 1).

Human metabolic studies show a limited conversion of ALA to DHA, typically below 5% in adult males [35–38.]Women have a greater efficiency of conversion than men [39] and this may be important for foetal supply during pregnancy. Women demonstrated lower omega -3 fatty acid intake than men considering the same age categories [40]. Furthermore, in addition to the limited conversion, there is also an age-related decrease in delta-6-desaturase activity, which is higher in women. These studies suggest that a supply of preformed EPA and DHA may be the best way to ensure adequate intake especially in ageing. Indeed, the shift in modern diets towards reduced omega-3 PUFA intake increases omega-6 PUFA consumption and if combined with less physical activity has a detrimental impact on development and aging, especially with regard to cognitive function [14].

Current guidelines are in the range of 250 to 500 mg EPA plus DHA per day [41]. However, most people do not consume enough omega-3 PUFAs, as indicated by average modern daily dietary DHA intakes that are closer to 100 mg per day; the optimal dietary omega-6 to omega-3 PUFA ratio is 2:1 and below, while the current Western diet is typically in the range of 10:1 to 25:1 [14].

The DHA dosage for achieving a significant response is another issue that requires further studies. For instance, in order to achieve 2 g/die of DHA [42], a daily meal of 135 g of Atlantic salmon may be required (Table 1). Therefore, it would be difficult to achieve such high DHA intakes without supplements [7].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

Table 1. Amount of ALA, EPA and DHA.

Food	ALA g/portion	EPA g/portion	DHA g/portion
Baked beans, canned, vegetarian	0.07		
Black walnuts	0.76		
Bread, whole wheat	0.04		
Canola oil	1.28		
Chia seeds	5.06		
Chicken, breast, roasted,		0.01	0.02
Cod, Pacific, cooked*		0.04	0.10
Edamame, frozen, prepared	0.28		
Egg, cooked			0.03
English walnuts	2.57		
Flaxseed oil	7.26		
Flaxseed, whole	2.35		
Ground beef, 85% lean, cooked**	0.04		
Herring, Atlantic, cooked*		0.77	0.94
Kidney beans, canned	0.10		
Lobster, cooked*	0.04	0.10	0.07
Mackerel, Atlantic, cooked*		0.43	0.59
Mayonnaise	0.74		
Milk, low-fat (1%)	0.01		
Oysters, eastern, wild, cooked,	0.14	0.30	0.23
Refried beans, canned, vegetarian	0.21		
Salmon, Atlantic, farmed, cooked		0.59	1.24
Salmon, Atlantic, wild, cooked		0.35	1.22
Salmon, pink, canned, drained*	0.04	0.28	0.63
Sardines, canned in tomato sauce, drained*		0.45	0.74
Scallops, cooked*		0.06	0.09
Sea bass, cooked *		0.18	0.47
Shrimp, cooked*		0.12	0.12
Soybean oil	0.92		
Tilapia, cooked*	0.04		0.11
Trout, rainbow, wild, cooked		0.40	0.44
Tuna, light, canned in water, drained*		0.02	0.17
Tuna, yellowfin, cooked*		0.01	0.09

*Except as noted, the USDA database does not specify whether fish are farmed or wild caught. **The United States Department of Agriculture Food Composition Databases does not specify whether beef is grass fed or grain fed. Data from Office of Dietary Supplements, National Institute of Health (NIH) [43,44].

2. Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra, pars compacta. A pathological hallmark of the disease is also the presence of Lewy bodies, which are intracellular inclusions enriched in the protein α-synuclein.

The common symptoms include tremor, rigidity, bradykinesia and postural insecurity, with dementia and depression observed in the advanced stages of the disease [30]. In a significant number of cases, depression appeared before the expression of Parkinson's classic symptoms, even previous to any evidence of motor impairment. Moreover, a recent study observed that people diagnosed with depression are three fold more

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

inclined to develop PD [45]. One-third of PD patients suffer depression that may lead to worse health outcomes and to a decreased quality of life. Anxiety, apathy and anhedonia further complicate PD outcomes [30].

Although the aetiology is currently unknown, there are a number of putative risk factors (e.g. exposure to environmental toxins) [46] and the pathogenic mechanisms include mitochondrial dysfunction, neuroinflammation and oxidative stress [47]. However, numerous studies support that a diet rich in PUFAs or supplementation with food products containing EPA and DHA could alleviate some of the patients' symptoms. The main scales used to evaluate PD symptoms are summarized in Table 2.

Table 2. Summary of main scales used for assessment of Parkinson's and Alzheimer's Disease ([48] with modifications).

Main scales	Description
Activities of Daily Living ADCS-ADL; ADCS-IADL	It measures the functional ability to perform activities of daily life. ADL assess basic living skills such as bathing and eating, whereas IADL measure more complex tasks such as using the telephone or preparing meals. A higher ADL or IADL score indicates a worsening functionality.
Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)	Is a sensitive and reliable method for the assessment of cognitive function in dementias. It consists of a psychometric scale of 11 items, and scores range from 0 (no impairment) to 70 (very severe impairment).
Beck Depression Inventory (BDI)	It is a 21-question multiple-choice self-report inventory, one of the most widely used psychometric tests for measuring the severity of depression.
Brief Assessment Schedule Depression Cards (BASDEC)	It is a brief test for screening depression, requiring minimal training to administer.
Bristol's Activities of Daily Living Scale (BADLS)	It is specifically designed for individuals with mild dementia living in the community for completion by caregivers.
Clinical Dementia Rating (CDR)	It is a global measure that assesses memory, orientation, judgment, and other features. Is based on caregiver interview. Classifies dementia into questionable, mild, moderate, and severe.
Clinical Global Impression Scale (CGI)	It measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders.
Clinician Interview-Based Impression of Change, plus carer interview (CIBIC-Plus)	It is a global measure capable of detecting changes in cognition, functionality, and behavior, thus assessing dementia's severity and progression. Requires separate interviews with patients and caregivers.
Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)	Is the handbook used by health care professionals in the United States and much of the world as the authoritative guide to the diagnosis of mental disorders.
Hamilton Depression Rating Scale (HDRS)	Is the most widely used clinician-administered depression assessment scale. The original version contains 17 items pertaining to symptoms of depression experienced over the past week.
Hoehn and Yahr scale	It is a commonly used system for describing how the symptoms of PD progress.
Hopkins Verbal Learning Test–Revised (HVLT-R)	It is a brief verbal learning and memory test ideal in situations calling for repeated neuropsychological examinations.
Mini-Mental State Examination (MMSE)	It evaluates cognitive function in the areas of orientation, memory, attention, calculation, language, and visual construction. It is widely translated and used in clinical practice. Patients score between 0 and 30 points, and cutoffs of 23/24 have typically been used to show significant cognitive impairment.
Montgomery–Åsberg Depression Rating Scale (MADRS)	Is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders.
Neuropsychiatric Inventory (NPI)	It assesses dementia-related behavioral symptoms. The NPI originally examined 10 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

	irritability/lability, and aberrant motor activity.
Neuropsychological test battery (NTB)	This scale assesses changes in cognitive function and is seen as a promising method for mild AD. NTB has shown to be able to detect changes in memory performance.
Unified Parkinson's Disease Rating Scale (UPDRS)	It evaluates of motor impairment and disability of patients with PD.

2.1. The role of omega-3 polyunsaturated fatty acids in PD: observational studies

The first major prospective study concerning environmental, life-style, and physical precursors of clinical Parkinson's disease is the Honolulu-Asia Aging Study [49], which started in 1965 and included a cohort of 8,006 Japanese-American men, during a 30-year follow-up. Among the dietary factors showing an inverse association with PD, the polyunsaturated fats [49] were included (Table 3).

Table 3. Prospective observational studies assessing the impact of omega-3 fatty acids supplementation in PD patients.

N° Patients	Population characteristic	Type and dose supplementation	Exposure period	Results	References
8006	PD Honolulu-Asia Aging Study	Food frequency questionnaire	30 years	PUFAs appeared protective.	[49]
5289	PD Rotterdam Study The Netherland	Semiquantitative food frequency questionnaire	6 years	Intakes of PUFAs were significantly associated with a lower risk of PD.	[50]
131.368	PD Health Professionals Follow-Up Study and the Nurses' Health Study USA	Semiquantitative food frequency questionnaire	16 years	High intakes of fruit, vegetables, whole grains, legumes, poultry, and fish was associated with a lower risk of PD.	[51]
249	PD Japan	Self-administered diet history questionnaire	6 years	Consumption of omega-3 PUFA, ALA, EPA, DHA were not associated with PD.	[52]

In The Rotterdam Study the intakes of total fats, MUFAs and PUFAs were significantly associated with a lower risk of PD, by means of energy-adjusted intake of fat and fatty acids [50].
The Health Professionals Follow-Up Study (1986–2002) and the Nurses' Health Study (1984–2000), including 131.368 men and women, evaluated the associations between dietary patterns and risk of PD. The main components analysis identified two dietary patterns: prudent and Western. The prudent dietary pattern, characterized by high intakes of fruit, vegetables and fish, was inversely associated with PD risk, but the Western pattern was not [51].
However a case-control study, which examined the relationship between dietary intake of individual fatty acids and the risk of PD in Japan, including 249 cases within 6 years of onset of PD, demonstrated that intake of omega-3 polyunsaturated fatty acids were not associated with PD. Higher consumption of ARA and cholesterol, instead, may be related to an increased risk of PD [52].
In summary we can conclude that prospective observational studies showed an association between a diet rich in polyunsaturated omega-3 fatty acids with a lower risk of PD.

2.2. The role of omega-3 polyunsaturated fatty acids in PD: randomized, double-blind, placebo-controlled clinical trials

Randomized, double-blind, placebo-controlled clinical trials involving PD are few for several reasons: poor

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

patient adherence to diet therapy, duration of dietary treatment, control of clinical parameters and evaluation of these same parameters. When the pathology occurs, already 70% of neurons are compromised; thus thinking that only a dietary treatment can restore brain functions is really an utopia. However, dietary treatments with omega-3 fatty acids may have advantages in reducing inflammation and, consequently, depressive symptoms.

Indeed, treatment for 6 months with 800 mg/day DHA and 290 mg/day EPA from fish oil, demonstrated, in the DHA treated patients, a reduction of 50% in the Hamilton Rating Scale for Depression (HDRS) total score if compared with the placebo group which took corn oil. DHA integration reduced the depressive symptoms [53]. However, treatment had no statistically significant effect on rate of change on either Unified Parkinson's Disease Rating Scale (UPDRS) or Hoehn-Yahr Scale score [53] (Table 4).

Table 4. Clinical trials assessing the impact of omega-3 fatty acids supplementation in PD patients.

N° Patients	Population characteristics	Type and dose supplementation	Exposure period	Results	References
24	PD Italy	800 mg/die DHA + 290 mg/die EPA from fish oil Placebo: corn oil	6 months	Treatment had no statistically significant effect on rate of change on either UPDRS or Hoehn-Yahr Scale score. In DHA-treated patients the HDRS score was reduced by at least 50%.	[53]
31	PD and Major Depression (DSM-IV) Brazil	480 mg/die DHA + 720 mg/die EPA from fish oil + tocopherol Placebo: mineral oil	3 months	Treatment had no statistically significant effect on rate of change on Hoehn-Yahr Scale score, but a significant decrease in MADRS and CGI scores.	[45]
60	PD Iran	1000 mg omega-3 fatty acids from flaxseed oil + 400 IU vitamin E Placebo: not specified	3 months	Treatment had favorable effects on UPDRS score.	[54]

Another double-blind, placebo-controlled study analyzed the effect of fish oil supplementation in parkinsonian patients with depression measured using Montgomery–Asberg Rating Scale (MADRS), the Clinical Global Impressions Scale (CGI) and Beck Depression Inventory (BDI) [45]. After 3 months, the supplementation of 4 capsules of omega-3 from fish oil (each capsule containing 180 mg EPA, 120 mg DHA and tocopherol) showed a significant decrease in MADRS and CGI-Depression scores while there was no difference among treated and control groups in BDI [45]. Moreover, Parkinson's symptoms, measured by Hoehn and Yahr scale, did not show significant variation during the 3 months of supplementation in all groups observed [45].

A randomized double-blind placebo-controlled clinical trial, conducted in 60 patients with PD, receiving either 1000 mg omega-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements or placebo for 3 months, showed that the dietetic supplementation in people with PD improved UPDRS compared with the placebo [54].

The published papers give an important indication on the use of omega-3 supplements especially for depression in PD; however, the number of patients recruited is small and also the type of supplement varies. It is widely demonstrated that the effective dose is 1 g/day of DHA. Animal or algal sources ensure a correct intake of DHA, while plant sources are often ineffective, since only 10% of ALA is metabolised to DHA. Despite this, the supplementation of omega 3 from linseed oil and vitamins E had favorable effects not only

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

on UPDRS but also on high-sensitivity C-reactive protein (hs-CRP), total antioxidant capacity (TAC), glutathione and markers of insulin metabolism [54]. Furthermore, the 3-6 month treatment is a relatively short period considering that we deal with dietary intervention in a pathology where the main symptoms are already evident [45,53,54].

3. Alzheimer's Disease

Alzheimer's Disease is a neurodegenerative disorder that accounts for the majority of cases of dementia, affecting over 35 million people worldwide. Some of the more usual clinical features include cognitive impairment, memory loss, language disorders, sudden changes of mood and behavior, and disorientation in time and space, hindering the patient's ability to perform normal daily activities. The neurodegenerative process observed in AD is usually present in patients' brain before the appearance of the first symptoms [55]. AD key features are the presence of neurofibrillary tangles and senile plaques and neuronal loss, resulting in cerebral atrophy.

Neurofibrillary tangles are composed of abnormal tau protein aggregates. Under normal conditions, tau protein contributes to the cytoskeleton structure by interacting with tubulin in order to stabilise the microtubule network. However, it may suffer different post-transcriptional modifications, such as truncation or hyperphosphorylation. Although the reasons that motivate these modifications remain elusive, there is compelling evidence that this hyperphosphorylated form is prone to aggregate, leading to the formation of neurofibrillary tangles that constitute toxic intracellular accumulations, mainly located in the hippocampus. Moreover, tau protein malfunction produces cytoskeleton destabilisation due to microtubule collapse, prompting synaptic failure that results in a loss of communication, thus contributing to AD-mediated neurodegeneration.

Since mitochondrial transport depends on its interactions with microtubules, this process is hindered upon tau hyperphosphorylation, causing energy deficits in presynaptic areas that may lead to synaptic disruption.

Senile plaques consist of extracellular deposits of β-amyloid peptide (Aβ), originating from amyloid precursor protein (APP) degradation. Such deposits cause inflammation and neuronal death. APP is a transmembrane protein present in neurons, which can be processed following two different routes: the amyloidogenic and the non-amyloidogenic pathways, both mediated by secretases: β- and γ-secretases take part in the first one, while α- and γ-secretases in the second one (Figure 2) [55]. In the non-amyloidogenic route, APP is sequentially cleaved by α-secretase and γ -secretase, giving rise to truncated peptides, $A\beta_{17–40/42}$ (Figure 2). In the amyloidogenic route, on the other hand, the sequential cleavage is carried out by β-secretase and γ-secretase, leading to whole-length Aβ peptides, responsible for the formation of the plaques. Both routes yield an amino-terminal fragment (APPsα for the non-amyloidogenic route and APPsβ for the amyloidogenic route) and a carboxy-terminal one (C83 and C99, respectively). The action of γ-secretase generates the APP intracellular domain (AICD), which participates in the cellular signalling. Depending on the point where γ-secretase performs the cut in the amyloidogenic route, the whole-length Aβ peptide would have a different dimension, with $A\beta_{1–40}$ and $A\beta_{1–42}$ being the dominant fragments in the brain (Figure 2) [55]. It has been shown that DHA increases the non-amyloidogenic processing resulting in an elevated α-secreted APP level by an increase in ADAM17 protein levels, caused by upregulated gene expression and decreased protein degradation. Additionally, DHA attenuates amyloidogenic processing affecting both β- and γ-secretase activity by independent mechanisms [56].

3.1. The role of omega-3 polyunsaturated fatty acids in AD: observational studies

The strongest support for a causal association between low fish and/or low DHA intake in AD comes from prospective epidemiological studies conducted in the Netherlands, USA and France. Of the 7 prospective studies that have been published, most show that higher intake of fish or omega-3 PUFA decreases the risk of AD (Table 5) [57].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

Table 5. Prospective observational studies assessing the impact of omega-3 fatty acids supplementation in AD patients.

N° Patients	Population characteristic	Type and dose supplementation	Exposure period	Results	References
5386	AD 37 Rotterdam Study The Netherland	Semiquantitative food frequency questionnaire	2.1 years	Fish consumption, an important source of omega 3 PUFA, was inversely related to incident dementia in particular to Alzheimer's disease.	[58]
815	AD 131 Chicago Health and Aging Project USA	Food frequency questionnaire	3.9 years	Dietary intake of omega 3 PUFA and weakly consumption of fish may reduce the risk of Alzheimer's disease.	[59]
2233	AD 190 Cardiovascular Health Cognition Study (CHCS) USA	Food frequency questionnaire	5.4 years	Consumption of fatty fish more than twice per week was associated with a reduction in risk of Alzheimer's disease by 41%.	[60]
488	AD not reported The Framingham Heart Study USA	Semiquantitative food frequency questionnaire	9.1 years	Plasma DHA level was associated with a significant 47% reduction in the risk of developing all-cause dementia.	[61]
8085	AD 183 Three-City cohort study France	Food frequency questionnaire	3.48 years	Frequent consumption of fruits and vegetables, fish, and omega 3 rich oils may decrease the risk of dementia and Alzheimer disease, especially among ApoE ε4 noncarriers.	[62]
5395	Rotterdam Study The Netherland	Semiquantitative food frequency questionnaire	9.6 years	In this cohort with a moderate consumption of fish and omega-3 PUFAs these dietary factors did not appear to be associated with long-term dementia risk	[63]
923	AD Rush Memory and Aging Project USA	Semiquantitative food frequency questionnaire	4.5 years	High adherence to all three diets may reduce AD risk.	[64]

The Rotterdam Study was the first to report that fish intake was inversely related to incident dementia in particular to Alzheimer's disease [58]. The data are confirmed by subsequent studies where the consumption of omega 3 [59] or fatty fish [60] or adherence to a diet rich in fruit, vegetables, fish and oils rich in omega 3 [62,64], is associated with a reduction in AD risk. Only a study published by Devore et al. [63] showed that a moderate consumption of fish and omega 3 PUFAs, do not appear to be associated with long-term dementia risk.

3.2. The role of omega-3 polyunsaturated fatty acids in AD: randomized, double-blind, placebo-controlled clinical trials

The first randomized clinical trial controlled by placebo (OmegAD Study) that evaluated omega-3 fatty acids' impact in AD was published in 2006 [65] (Table 6).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

Table 6. Clinical trials assessing the impact of omega-3 fatty acids supplementation in AD patients.

N° Patients	Population characteristic	Type and dose supplementation	Exposure period	Results	References
204	AD (DSM-IV) MMSE 15-30 OmegAD Study	1720 mg/die DHA+ 600 mg/die EPA Placebo: 4000 mg corn oil Both groups: + 16 mg/die Vit.E	12 months	There was no significant statistical difference after 6 or 12 months treatment between groups in MMSE, ADAS-cog, CDR. A subgroup with very mild cognitive dysfunction showed a reduction in decline rate.	[65]
204	AD (DSM-IV) MMSE 15-30 OmegAD Study	1720 mg/die DHA+ 600 mg/die EPA Placebo: 4000 mg corn oil Both groups: + 16 mg Vit.E	12 months	Supplementation with omega-3 did not result in marked effects on neuropsychiatric symptoms except for possible positive effects on depressive symptoms (assessed by MADRS) in non-APOEε4 carriers and agitation symptoms (assessed by NPI) in APOEε4 carriers.	[66]
46	AD AD (DSM-IV) MMSE 10-26 CDR-score 1-2	720 mg/die DHA+ 1080 mg/die EPA Placebo: olive oil Both groups: + 1.2 mg hydroquinone + 12 mg tocopherols	6 months	Treated group did not show an improvement in cognitive symptoms measured by MMSE, ADAS-cog, HDR but a relative improvement in CIBIC-plus score. In a subgroup with subject with mild cognitive impairment (MMSE>27 e CDR 0.5-1) improvement in ADAS-cog.	[67]
402	AD MMSE 14-26 Alzheimer's Disease Cooperative Study (ADCS) DHA Supplementation Trial USA	2000 mg/die DHA from seaweed Placebo: corn or soy oil	18 months	Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer disease assessed by MMSE, ADAS-cog, CDR, ADS-ADL, NPI.	[68]
225	AD Souvenir I Study	1700 mg/die DHA+ 600 mg/die EPA (Souvenaid) Placebo: control drink	6 months	Supplementation with omega -3 improved delayed verbal recall. However ADAS-cog, CIBIC-plus, NPI, ADCS-ADL, ADSC-ADL were unchanged.	[69]
225	AD Souvenir I Study	1700 mg/die DHA+ 600 mg/die EPA (Souvenaid) Placebo: control drink	6 months	Souvenaid had a positive result on ADAS-cog outcome. A higher intake of Souvenaid was also associated with greater cognitive benefit.	[70]
238	AD Souvenir II Study	1200 mg/die DHA+ 300 mg/die EPA (Souvenaid) Placebo: control products	6 months	In active group the NTB memory domain increased.	[71]

527	AD MMSE 14 - 24 Connect Study	1200 mg/die DHA+ 300 mg/die EPA (Souvenaid) Placebo: control products	6 months	Cognitive performance as assessed by ADAS-cog showed decline over time in both control and active study groups, with no significant difference between study groups. Add-on intake of Souvenaid did not slow cognitive decline in persons treated for mild-to-moderate AD.	[72]
174	AD mild to moderate OmegAD Study	1720 mg/die DHA+ 600 mg /die EPA Placebo: 4000 mg corn oil	12 months	Plasma transthyretin positively correlated with MMSE and inversely with ADAS-Cog, suggesting a potential mechanism for probable positive effects of omega 3 on cognition.	[73]
39	AD MMSE 15-26 CDR 0.5-1.0 Not depressed (CESD <4.0)	675 mg/die DHA+ 975 mg /die EPA Group omega-3 plus alpha lipoic acid (LA): 675 mg/die DHA+ 975 mg/die EPA+ 600 mg/die LA Placebo: soy oil	12 months	Active groups were no different from placebo group in ADAS-cog, ADL. Omega-3 + LA group showed less decline assessed by MMSE. IADL differences between placebo e omega-3 and between placebo e omega 3+LA groups were observed.	[74]
179	AD mild Souvenir II Study	1700 mg/die DHA+ 6 mg/die EPA (Souvenaid) Placebo: control drink	6 months	The administration contributed to maintenance of the organization of brain networks in mild AD patients.	[75]
19	AD MMSE 16-30	625 mg/die DHA+ 600 mg/die EPA Placebo: olive oil Both groups: + 20 mg mixed tocopherols	4 months	The daily supplementation was associated with none or only negligible benefits on mood and cognition assessed by MMSE, HVLT-R, BASDEC, BADLS.	[76]
204	AD OmegAD Study	1720 mg/die DHA+ 600 mg/die EPA Placebo: 4000 mg corn oil Both groups: + 16 mg Vit.E	6 months	The daily supplementation stabilized the cognitive performance of AD subjects assessed by ADAS-cog and MMSE scores.	[77]
204	AD OmegAD Study	1720 mg/die DHA+ 600 mg/die EPA Placebo: 4000 mg corn oil Both groups: + 16 mg Vit.E	6 months	A decrease was observed in RvD1 and LXA4 production from peripheral blood mononuclear cells of AD patients who not received omega-3 but not in cells of AD subjects under omega-3 intake.	[78]
201	AD Open label extension study (OLE) Souvenir II	1200 mg/die DHA+ 300 mg/die EPA (Souvenaid) Placebo:	6 months	The intake of Souvenaid was well tolerated with a favorable safety profile. The adherence to Souvenaid was very high reflecting its good	[79]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

	MMSE≥20	control drink		tolerability and ease of use.	
171	AD OmegAD Study	1720 mg/die DHA+ 600 mg/die EPA Placebo: 1 g corn oil Both groups: + 16 mg Vit.E	6 months	The effect of omega-3 supplementation on MMSE and CDR appeared to be influenced by homocysteine plasma levels.	[80]

Freund-Levi et al. [65] assessed omega-3 fatty acids' supplementation in 204 subjects with mild to moderate AD. The treated group received omega-3 fatty acids in the daily dosages of 1720 mg DHA and 600 mg EPA and the placebo group received 4000 mg of corn oil (containing 2400 mg LA) for 6 months, followed by additional 6 months of omega-3 fatty acids' supplementation for both groups. Medication for AD treatment was allowed. As a result, there was no significant statistical difference after a 6 - or 12-month treatment between groups in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog), Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR). In a subgroup with very mild AD (MMSE>27 and CDR 0.5–1), there was a significant reduction in decline rate between intervention and placebo groups in the first 6 months.

In a second paper published in 2008, Freund-Levi et al. [66], using the same sample from 2006, showed that supplementation with omega-3 in patients with mild to moderate AD did not result in marked effects on neuropsychiatric symptoms except from possible positive effects on depression (assessed by MADRS) in non-APOEε4 carriers and agitation symptoms (assessed by Neuropsychiatric Inventory, NPI) in APOEε4 carriers. The mechanism of action of omega-3 in the brain in relation to behavior is not fully understood. In rats, it has been shown that an increased intake of both EPA and DHA, whereas a combination of the two omega-3 PUFAs inhibit protein kinase C (PKC) activity after subchronic exposition in cell cultures. Well established mood stabilizers such as lithium and valproic acid are known to inhibit PKC activity. Thus, inhibition of PKC may also represent a potential mode of action of omega-3 in bipolar disorders. Other possible mechanisms could be that omega-3 fatty acids affect neurotransmitter levels and membrane fluidity also by decreasing production of pro inflammatory eicosanoids that might be elevated in depression [66].

Chiu et al. [67] studied 46 subjects with mild to moderate AD or mild cognitive impairment (DSM-IV: MMSE 10-26, CDR-score 1-2). During 6 months, intervention group received 720 mg/die DHA and 1080 mg/die EPA, while placebo group received olive oil. Medication for AD treatment was not allowed. There was no significant statistical difference in MMSE, ADAS-cog and HDRS between the two groups. The negative results of cognitive assessments support the previous studies by Freund-Levi et al. [65,66], and all of the studies showed there might be a positive effect of omega-3 fatty acids only in subgroups with mild cognitive deficits. A significant improvement was observed in Clinician Interview-Based Impression of Change, plus carer interview (CIBIC-plus) in the intervention group compared to placebo group. This might be accounted for the cognitive and behavioral components rather than the functional one. It has been suggested that omega-3 fatty acids may have beneficial effects on mood, although this is an unlikely explanation for these findings because of the stringent exclusion of people with significant depression and the lack of association with HDRS score. The relative improvement of general clinical conditions might have resulted from amelioration in other areas of health, such as cardiovascular or immunological systems on which beneficial effects of omega 3 PUFAs have been reported [67]. In a subgroup, participants with mild cognitive impairment (MMSE>27 e CDR 0.5-1) but not with AD, showed a significant additional delay in ADAS-cog decline compared to placebo group.

Quinn et al. [68] assessed 402 subjects with mild to moderate AD. The intervention group received DHA 2000 mg/die from seaweed and the placebo group received corn or soy oil for 18 months. Medication for AD treatment was allowed. Supplementation with DHA compared with placebo did not slow the rate of cognitive and functional decline in patients with mild to moderate Alzheimer's disease (no beneficial effect on rate of change on MMSE, ADAS-cog, CDR, ADS-ADL and NPI).

Sheltens et al. [69] assessed 225 subjects with mild AD. The intervention group received DHA 1700 mg/die

and EPA 600 mg/die from a medical food named Souvenaid and the placebo group received a control drink for 6 months. Significant improvement in the delayed verbal recall task was noted in the supplemented group compared with control. ADAS-cog and other outcome scores (CIBIC-plus, NPI, ADCS-ADL) remained unchanged.

The same authors published a study [70] where the same above-mentioned population was divided into two subgroups: patients with 'low' baseline ADAS-cog scores (<25.0) and patients with 'high' baseline ADAS-cog scores (≥25.0). Repeated measures models were used to determine the relationship between ADAS-cog score and intervention. Baseline ADAS-cog significantly influenced the effect of Souvenaid intervention on ADAS-cog outcome. A higher intake of the medical food was also associated with greater cognitive benefit.

Based on these results, two double-blind, randomized controlled clinical trials were designed. The Souvenir II study examined the effect of longer treatment duration (6 months) with Souvenaid as compared with control product on memory performance in drug-naïve mild AD [81]. Neuropsychological Test Battery (NTB) memory domain increased in active group.

Since the ADAS-cog may be more sensitive to change in moderate AD and since Souvenaid had not been tested in moderate AD patients already taking AD medications, a novel S-Connect study was designed. In this double-blind, parallel, randomized, controlled clinical study, the efficacy and tolerability of Souvenaid was investigated in 527 persons with mild to moderate AD taking stable doses of Souvenaid [72]. Cognitive performance as assessed by ADAS-cog showed decline over time in both control and active study groups, with no significant difference between study groups themselves. Intake of Souvenaid did not slow cognitive decline in persons treated for mild to moderate AD.

Faxen-Irving et al., as a part of a previously published study on a DHA rich supplementation to subjects with AD [65], explored the effects of transthyretin on plasma and CSF. Since plasma transthyretin correlated with MMSE and inversely with ADAS-Cog, these authors suggest a potential mechanism for probable positive effects of omega 3 on cognition.

Shinto et al. [74] studied 39 subjects with probable AD in a randomized placebo-controlled pilot with three arms. Two groups received omega 3 fatty acids' supplementation, one only omega-3 fatty acids (DHA 675 mg/die and EPA 975 mg/die), and the other with the addition of alpha lipoic acid (600 mg/die); placebo group received soy oil. The intervention lasted 12 months and medication for AD was allowed. There were no differences in ADAS-cog and ADL between placebo and omega-3 fatty acids or between placebo and omega-3 fatty acids + alpha lipoic acid. In MMSE, the mean alteration between placebo group and intervention group with only omega-3 fatty acids was not significant, whereas the difference between placebo and omega-3 fatty acids + alpha lipoic acid was significant. The mean alteration in IADL (Table 2) was significant between placebo group and omega-3 fatty acids' group and between placebo and omega-3 fatty acids + alpha lipoic acid.

In a secondary analysis of the Souvenir II study [75], results suggest that Souvenaid preserves the organisation of brain networks in patients with mild AD within 6 months, hypothetically counteracting the progressive network disruption over time in AD. These results strengthen the hypothesis that Souvenaid affects synaptic integrity and function.

Phillips et al. [76] assessed omega-3 fatty acids' supplementation in 19 subjects with AD. The intervention group received daily omega-3 fatty acids in the dosages of 625 mg DHA and 600 mg EPA and the placebo group received olive oil for 4 months. The daily supplementation was associated with none or only negligible benefits on mood and cognition assessed by MMSE, the Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Assessment Schedule Depression Cards (BASDEC) and Bristol's Activities of Daily Living Scale (BADLS).

Data obtained in the OmegAD study [66,82]were collected to examine the relationship of plasma omega-3 levels to cognitive scores (using ADAS-cog and the MMSE) [83]. The daily supplementation stabilizes the cognitive performance of AD subjects assessed by ADAS-cog and MMSE scores.

Also from the OmegAD study a decrease was observed in resolvin D1 (RvD1) and lipoxin A_4 (LXA_4) production from peripheral blood mononuclear cells of AD patients who did not receive omega-3 supplementation but not in cells of AD subjects under omega-3 intake [78].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

Recent systematic meta-analysis did not show any significant benefits of omega-3 fatty acids supplementation in the treatment of mild to moderate AD, even if the treatment did not raise any substantial safety issues [13]. In fact studies concerning the tolerability, safety and effect size of Souvenaid demonstrated that the use of medical food for up to 12 months was well tolerated, with a favorable safety profile and high adherence of intake [79,84]. Moreover the efficacy of omega-3 supplementation seems to be influenced by the baseline levels of plasma total homocysteine, suggesting that adequate B vitamin status is required to obtain beneficial effects of omega-3 on cognitive performance in moderate AD [80].

5. Materials and Methods

The authors searched PubMed, Web of Science and Scopus articles using a combination of "omega-3 fatty acids,", "Parkinson's Disease, "Alzheimer's Disease", "clinical trials" as keywords. Inclusion criteria consisted in original intervention studies, controlled by placebo, that assessed omega-3 polyunsaturated fatty acids impact on cognitive function in humans with PD or AD, until May 2019, without limitation for the initial date of publication. We searched for interventions using omega-3 polyunsaturated fatty acids as supplementation (in capsules, or in any other form than in food itself) or as increased dietary intake (throughout food sources, such as fish or fish oils). We first applied eligibility criteria in titles' analysis, followed by abstracts' analysis and full texts' reading. Search, selection, and information extraction were performed independently by two reviewers. In order to favor reliability, data were collected independently in a table including number of patients, population characteristics, type and dose of supplementation, exposure period, results and references. The authors prepared references using Zotero as bibliography software.

6. Conclusions

Neurodegenerative conditions, such as Parkinson's disease and Alzheimer's disease, represent a challenging issue in clinical medicine, and their burden is expected to increase dramatically in the forthcoming decades. At the present time no etiological treatment is routinely available and medical therapy is mainly symptomatic; the adoption of a nutritional approach would be highly recommendable.

Omega-3 fatty acids represent an interesting biological potential, in view of their anti-inflammatory and metabolic properties, in the management of these diseases.

Indeed, the evidence deriving from prospective observational studies is encouraging, both for Parkinson's and Alzheimer's disease. The adoption of a dietary regimen enriched in omega-3 fatty acids rather consistently associates with a reduced risk of either condition. On the other hand, randomized trials have provided conflicting results, and many of them have failed to document a definite protective effect. This was confirmed by most reviews and meta-analyses performed so far.

The inconsistency between observational and randomized studies is not unusual in clinical research, particularly when considering treatment with dietary supplements or integrators. A number of reasons may account for this finding. Firstly, in controlled trials dietary supplementation is usually carried out over a relatively limited time span, compared with the life-long exposure of real-life observational studies. Furthermore, and possibly more importantly, the variations in dietary patterns might reflect the adoption of a healthier lifestyle, in adjunct to the contribution provided by the single nutrient supplementation. This was postulated, for instance, when investigating the protective effects of the Mediterranean diet on cognitive performances. In the present context, intake of higher amounts of foods containing omega-3 fatty acids might associate with a reduced intake of other nutrients, such as meat.

Finally, the possibility of different individual responses to the dietary intervention must be considered. As mentioned in this review, the protective effects exerted by omega-3 fatty acids is likely to be modulated by patient-related factors, some of which may have a significant genetic component and may therefore be unmodifiable, and unpredictable with routine clinical and biochemical evaluation.

At any rate, treatment with omega-3 fatty acids was generally reported to be safe and well tolerated. In our

 doi:10.20944/preprints201907.0289.v1

opinion, they may indeed represent a valuable and biologically plausible tool in the management of neurodegenerative diseases. Of course, supplementation needs to be a part of a global lifestyle intervention, and has to take place in the early stages of the disease, when a benefit may be detected. Hopefully, in a near future the adoption of personalized treatment strategies, aimed to predict individual responses, will help to optimize the effectiveness of such intervention, in order to face the progressive rise of these devastating conditions.

Author Contributions: Conceptualization, R.A.; methodology, R.A., G.V. and M.B.; writing—original draft preparation, R.A.; writing—review and editing, G.V. and M.B.; supervision, M.B.; funding acquisition, G.V.

Funding: This work was supported by the Fondazione Cassa di Risparmio di Modena Grant n.2018.0334.

Acknowledgments: The authors would like to thank Dr. Lorenzo Corsi for his useful contribution to manuscript's figures.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

5-LOX	5-lipoxygenase
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADCS	Activities of Daily Living Scales
ALA	α–linolenic acid
ApoE	apolipoprotein E
APP	amyloid precursor protein
ARA	arachidonic acid
Aβ	amyloid beta peptide
BADLS	Bristol's Activities of Daily Living Scale
BASDEC	Brief Assessment Schedule Depression Cards
BBB	blood-brain barrier
BDI	Beck Depression Inventory Scale
CDR	Clinical Dementia Rating Scale
CGI	Clinical Global Impression Scale
CIBIC-Plus	Clinician Interview-Based Impression of Change, plus carer interview
COX	cyclooxygenase
cPLA2	cytosolic calcium-dependent phospholipase A2
CSF	cerebrospinal fluid
DHA	docosahexaenoic acid
DHA-FFA	free nonesterified form docosahexaenoic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EPA	eicosapentaenoic acid
FABPs	fatty acid binding proteins
HDRS	Hamilton Depression Rating Scale
hs-CRP	C-reactive protein
HVLT-R	Hopkins Verbal Learning Test–Revised
iPLA2	cytosolic calcium-independent phospholipase A2
LA	linoleic acid
LXA_4	lipoxin A_4
MADRS	Montgomery–Åsberg Depression Rating Scale
MMSE	Mini-Mental State Examination
MUFAs	monounsaturated fatty acids
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological test battery

 doi:10.20944/preprints201907.0289.v1

PD	Parkinson's disease
PKC	protein kinase C
PLA2	phospholipase A2
PUFAs	omega-3 polyunsaturated fatty acids
sPLA2	secretory phospholipase A2
RvD1	resolvin D1
TAC	total antioxidant capacity
UPDRS	Unified Parkinson's Disease Rating Scale

References

1. Cansev, M.; Wurtman, R. J.; Sakamoto, T.; Ulus, I. H. Oral Administration of Circulating Precursors for Membrane Phosphatides Can Promote the Synthesis of New Brain Synapses. *Alzheimers Dement. J. Alzheimers Assoc.* **2008**, *4* (Supplement 1), s153–s168. https://doi.org/10.1016/j.jalz.2007.10.005.
2. Beltz, B. S.; Tlusty, M. F.; Benton, J. L.; Sandeman, D. C. Omega-3 Fatty Acids Upregulate Adult Neurogenesis. *Neurosci. Lett.* **2007**, *415* (2), 154–158. https://doi.org/10.1016/j.neulet.2007.01.010.
3. Kawakita, E.; Hashimoto, M.; Shido, O. Docosahexaenoic Acid Promotes Neurogenesis in Vitro and in Vivo. *Neuroscience* **2006**, *139* (3), 991–997. https://doi.org/10.1016/j.neuroscience.2006.01.021.
4. Cutuli, D. Functional and Structural Benefits Induced by Omega-3 Polyunsaturated Fatty Acids During Aging. *Curr. Neuropharmacol.* **2017**, *15* (4), 534–542. https://doi.org/10.2174/1570159X14666160614091311.
5. Aryal, S.; Hussain, S.; Drevon, C. A.; Nagelhus, E.; Hvalby, Ø.; Jensen, V.; Walaas, S. I.; Davanger, S. Omega-3 Fatty Acids Regulate Plasticity in Distinct Hippocampal Glutamatergic Synapses. *Eur. J. Neurosci.* **2019**, *49* (1), 40–50. https://doi.org/10.1111/ejn.14224.
6. Castro-Gómez, P.; Garcia-Serrano, A.; Visioli, F.; Fontecha, J. Relevance of Dietary Glycerophospholipids and Sphingolipids to Human Health. *Prostaglandins Leukot. Essent. Fatty Acids* **2015**, *101*, 41–51. https://doi.org/10.1016/j.plefa.2015.07.004.
7. Cardoso, C.; Afonso, C.; Bandarra, N. M. Dietary DHA and Health: Cognitive Function Ageing. *Nutr. Res. Rev.* **2016**, *29* (2), 281–294. https://doi.org/10.1017/S0954422416000184.
8. Calviello, G.; Su, H.-M.; Weylandt, K. H.; Fasano, E.; Serini, S.; Cittadini, A. Experimental Evidence of ω-3 Polyunsaturated Fatty Acid Modulation of Inflammatory Cytokines and Bioactive Lipid Mediators: Their Potential Role in Inflammatory, Neurodegenerative, and Neoplastic Diseases. *BioMed Res. Int.* **2013**, *2013*, 743171. https://doi.org/10.1155/2013/743171.
9. Moore, K.; Hughes, C. F.; Ward, M.; Hoey, L.; McNulty, H. Diet, Nutrition and the Ageing Brain: Current Evidence and New Directions. *Proc. Nutr. Soc.* **2018**, *77* (2), 152–163. https://doi.org/10.1017/S0029665117004177.
10. Yassine, H. N.; Braskie, M. N.; Mack, W. J.; Castor, K. J.; Fonteh, A. N.; Schneider, L. S.; Harrington, M. G.; Chui, H. C. Association of Docosahexaenoic Acid Supplementation With Alzheimer Disease Stage in Apolipoprotein E E4 Carriers: A Review. *JAMA Neurol.* **2017**, *74* (3), 339–347. https://doi.org/10.1001/jamaneurol.2016.4899.
11. Araya-Quintanilla, F.; Gutiérrez-Espinoza, H.; Sánchez-Montoya, U.; Muñoz-Yañez, M. J.; Baeza-Vergara, A.; Petersen-Yanjarí, M.; Fernández-Lecaros, L. Effectiveness of Omega-3 Fatty Acid Supplementation in Patients with Alzheimer Disease: A Systematic Review and Meta-Analysis. *Neurol. Barc. Spain* **2017**. https://doi.org/10.1016/j.nrl.2017.07.009.
12. Butler, M.; Nelson, V. A.; Davila, H.; Ratner, E.; Fink, H. A.; Hemmy, L. S.; McCarten, J. R.; Barclay, T. R.; Brasure, M.; Kane, R. L. Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. *Ann. Intern. Med.* **2018**, *168* (1), 52–62. https://doi.org/10.7326/M17-1530.
13. Burckhardt, M.; Herke, M.; Wustmann, T.; Watzke, S.; Langer, G.; Fink, A. Omega-3 Fatty Acids for the Treatment of Dementia. *Cochrane Database Syst. Rev.* **2016**, *4*, CD009002. https://doi.org/10.1002/14651858.CD009002.pub3.
14. Weiser, M. J.; Butt, C. M.; Mohajeri, M. H. Docosahexaenoic Acid and Cognition throughout the Lifespan. *Nutrients* **2016**, *8* (2), 99. https://doi.org/10.3390/nu8020099.
15. Chappus-McCendie, H.; Chevalier, L.; Roberge, C.; Plourde, M. Omega-3 PUFA Metabolism and Brain Modifications during Aging. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *94*, 109662. https://doi.org/10.1016/j.pnpbp.2019.109662.
16. Brenna, J. T.; Diau, G.-Y. The Influence of Dietary Docosahexaenoic Acid and Arachidonic Acid on Central Nervous System Polyunsaturated Fatty Acid Composition. *Prostaglandins Leukot. Essent. Fatty Acids* **2007**, *77* (5–6), 247–250. https://doi.org/10.1016/j.plefa.2007.10.016.
17. Wassall, S. R.; Leng, X.; Canner, S. W.; Pennington, E. R.; Kinnun, J. J.; Cavazos, A. T.; Dadoo, S.; Johnson, D.; Heberle, F. A.; Katsaras, J.; et al. Docosahexaenoic Acid Regulates the Formation of Lipid Rafts: A Unified View from Experiment and Simulation. *Biochim. Biophys. Acta Biomembr.* **2018**, *1860* (10), 1985–1993. https://doi.org/10.1016/j.bbamem.2018.04.016.
18. Uauy, R.; Dangour, A. D. Nutrition in Brain Development and Aging: Role of Essential Fatty Acids. *Nutr. Rev.* **2006**, *64* (5 Pt 2), S24-33; discussion S72-91. https://doi.org/10.1301/nr.2006.may.s24-s33.
19. de Bus, I.; Witkamp, R.; Zuilhof, H.; Albada, B.; Balvers, M. The Role of N-3 PUFA-Derived Fatty Acid Derivatives and Their Oxygenated Metabolites in the Modulation of Inflammation. *Prostaglandins Other Lipid Mediat.* **2019**, *144*, 106351. https://doi.org/10.1016/j.prostaglandins.2019.106351.

20. Janssen, C. I. F.; Kiliaan, A. J. Long-Chain Polyunsaturated Fatty Acids (LCPUFA) from Genesis to Senescence: The Influence of LCPUFA on Neural Development, Aging, and Neurodegeneration. *Prog. Lipid Res.* **2014**, *53*, 1–17. https://doi.org/10.1016/j.plipres.2013.10.002.
21. Simopoulos, A. P. The Omega-6/Omega-3 Fatty Acid Ratio, Genetic Variation, and Cardiovascular Disease. *Asia Pac. J. Clin. Nutr.* **2008**, *17 Suppl 1*, 131–134.
22. Schmitz, G.; Ecker, J. The Opposing Effects of N-3 and n-6 Fatty Acids. *Prog. Lipid Res.* **2008**, *47* (2), 147–155. https://doi.org/10.1016/j.plipres.2007.12.004.
23. Chevalier, L.; Chappus-McCendie, H.; Roberge, C.; Plourde, M. Omega-3 PUFA Metabolism and Brain Modifications during Aging. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, 109662. https://doi.org/10.1016/j.pnpbp.2019.109662.
24. Chen, S.; Subbaiah, P. V. Regioisomers of Phosphatidylcholine Containing DHA and Their Potential to Deliver DHA to the Brain: Role of Phospholipase Specificities. *Lipids* **2013**, *48* (7), 675–686. https://doi.org/10.1007/s11745-013-3791-5.
25. Liu, R.-Z.; Mita, R.; Beaulieu, M.; Gao, Z.; Godbout, R. Fatty Acid Binding Proteins in Brain Development and Disease. *Int. J. Dev. Biol.* **2010**, *54* (8–9), 1229–1239. https://doi.org/10.1387/ijdb.092976rl.
26. Pan, Y.; Scanlon, M. J.; Owada, Y.; Yamamoto, Y.; Porter, C. J. H.; Nicolazzo, J. A. Fatty Acid-Binding Protein 5 Facilitates the Blood-Brain Barrier Transport of Docosahexaenoic Acid. *Mol. Pharm.* **2015**, *12* (12), 4375–4385. https://doi.org/10.1021/acs.molpharmaceut.5b00580.
27. Vandal, M.; Alata, W.; Tremblay, C.; Rioux-Perreault, C.; Salem, N.; Calon, F.; Plourde, M. Reduction in DHA Transport to the Brain of Mice Expressing Human APOE4 Compared to APOE2. *J. Neurochem.* **2014**, *129* (3), 516–526. https://doi.org/10.1111/jnc.12640.
28. Ouellet, M.; Emond, V.; Chen, C. T.; Julien, C.; Bourasset, F.; Oddo, S.; LaFerla, F.; Bazinet, R. P.; Calon, F. Diffusion of Docosahexaenoic and Eicosapentaenoic Acids through the Blood-Brain Barrier: An in Situ Cerebral Perfusion Study. *Neurochem. Int.* **2009**, *55* (7), 476–482. https://doi.org/10.1016/j.neuint.2009.04.018.
29. Chen, C. T.; Green, J. T.; Orr, S. K.; Bazinet, R. P. Regulation of Brain Polyunsaturated Fatty Acid Uptake and Turnover. *Prostaglandins Leukot. Essent. Fatty Acids* **2008**, *79* (3–5), 85–91. https://doi.org/10.1016/j.plefa.2008.09.003.
30. Zárate, R.; El Jaber-Vazdekis, N.; Tejera, N.; Pérez, J. A.; Rodríguez, C. Significance of Long Chain Polyunsaturated Fatty Acids in Human Health. *Clin. Transl. Med.* **2017**, *6* (1), 25. https://doi.org/10.1186/s40169-017-0153-6.
31. Murakami, M. Lipoquality Control by Phospholipase A2 Enzymes. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2017**, *93* (9), 677–702. https://doi.org/10.2183/pjab.93.043.
32. Innes, J. K.; Calder, P. C. Omega-6 Fatty Acids and Inflammation. *Prostaglandins Leukot. Essent. Fatty Acids* **2018**, *132*, 41–48. https://doi.org/10.1016/j.plefa.2018.03.004.
33. Tassoni, D.; Kaur, G.; Weisinger, R. S.; Sinclair, A. J. The Role of Eicosanoids in the Brain. *Asia Pac. J. Clin. Nutr.* **2008**, *17 Suppl 1*, 220–228.
34. Tapiero, H.; Ba, G. N.; Couvreur, P.; Tew, K. D. Polyunsaturated Fatty Acids (PUFA) and Eicosanoids in Human Health and Pathologies. *Biomed. Pharmacother. Biomedecine Pharmacother.* **2002**, *56* (5), 215–222.
35. Dyall, S. C.; Michael-Titus, A. T. Neurological Benefits of Omega-3 Fatty Acids. *Neuromolecular Med.* **2008**, *10* (4), 219–235. https://doi.org/10.1007/s12017-008-8036-z.
36. Pawlosky, R. J.; Hibbeln, J. R.; Novotny, J. A.; Salem, N. Physiological Compartmental Analysis of Alpha-Linolenic Acid Metabolism in Adult Humans. *J. Lipid Res.* **2001**, *42* (8), 1257–1265.
37. Brenna, J. T. Efficiency of Conversion of Alpha-Linolenic Acid to Long Chain n-3 Fatty Acids in Man. *Curr. Opin. Clin. Nutr. Metab. Care* **2002**, *5* (2), 127–132.
38. Burdge, G. C.; Wootton, S. A. Conversion of Alpha-Linolenic Acid to Eicosapentaenoic, Docosapentaenoic and Docosahexaenoic Acids in Young Women. *Br. J. Nutr.* **2002**, *88* (4), 411–420. https://doi.org/10.1079/BJN2002689.
39. Burdge, G. C. Metabolism of Alpha-Linolenic Acid in Humans. *Prostaglandins Leukot. Essent. Fatty Acids* **2006**, *75* (3), 161–168. https://doi.org/10.1016/j.plefa.2006.05.013.
40. Thompson, M.; Hein, N.; Hanson, C.; Smith, L. M.; Anderson-Berry, A.; Richter, C. K.; Stessy Bisselou, K.; Kusi Appiah, A.; Kris-Etherton, P.; Skulas-Ray, A. C.; et al. Omega-3 Fatty Acid Intake by Age, Gender, and Pregnancy Status in the United States: National Health and Nutrition Examination Survey 2003-2014. *Nutrients* **2019**, *11* (1). https://doi.org/10.3390/nu11010177.
41. Scientific Opinion on the Tolerable Upper Intake Level of Eicosapentaenoic Acid (EPA), Docosahexaenoic Acid (DHA) and Docosapentaenoic Acid (DPA). *EFSA J.* **2012**, *10* (7), 2815. https://doi.org/10.2903/j.efsa.2012.2815.
42. Ghasemi Fard, S.; Wang, F.; Sinclair, A. J.; Elliott, G.; Turchini, G. M. How Does High DHA Fish Oil Affect Health? A Systematic Review of Evidence. *Crit. Rev. Food Sci. Nutr.* **2019**, *59* (11), 1684–1727. https://doi.org/10.1080/10408398.2018.1425978.

43. Nguyen, Q. V.; Malau-Aduli, B. S.; Cavalieri, J.; Nichols, P. D.; Malau-Aduli, A. E. O. Enhancing Omega-3 Long-Chain Polyunsaturated Fatty Acid Content of Dairy-Derived Foods for Human Consumption. *Nutrients* **2019**, *11* (4). https://doi.org/10.3390/nu11040743.
44. Office of Dietary Supplements - Omega-3 Fatty Acids https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/ (accessed Jun 7, 2019).
45. da Silva, T. M.; Munhoz, R. P.; Alvarez, C.; Naliwaiko, K.; Kiss, Á.; Andreatini, R.; Ferraz, A. C. Depression in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Pilot Study of Omega-3 Fatty-Acid Supplementation. *J. Affect. Disord.* **2008**, *111* (2), 351–359. https://doi.org/10.1016/j.jad.2008.03.008.
46. Kamel, F.; Goldman, S. M.; Umbach, D. M.; Chen, H.; Richardson, G.; Barber, M. R.; Meng, C.; Marras, C.; Korell, M.; Kasten, M.; et al. Dietary Fat Intake, Pesticide Use, and Parkinson's Disease. *Parkinsonism Relat. Disord.* **2014**, *20* (1), 82–87. https://doi.org/10.1016/j.parkreldis.2013.09.023.
47. Elfawy, H. A.; Das, B. Crosstalk between Mitochondrial Dysfunction, Oxidative Stress, and Age Related Neurodegenerative Disease: Etiologies and Therapeutic Strategies. *Life Sci.* **2019**, *218*, 165–184. https://doi.org/10.1016/j.lfs.2018.12.029.
48. Canhada, S.; Castro, K.; Perry, I. S.; Luft, V. C. Omega-3 Fatty Acids' Supplementation in Alzheimer's Disease: A Systematic Review. *Nutr. Neurosci.* **2018**, *21* (8), 529–538. https://doi.org/10.1080/1028415X.2017.1321813.
49. Abbott, R. D.; Webster Ross, G.; White, L. R.; Sanderson, W. T.; Burchfiel, C. M.; Kashon, M.; Sharp, D. S.; Masaki, K. H.; Curb, J. D.; Petrovitch, H. Environmental, Life-Style, Andphysical Precursors of Clinical Parkinson's Disease: Recentfindings from the Honolulu-Asia Aging Study. *J. Neurol.* **2003**, *250* (3), iii30–iii39. https://doi.org/10.1007/s00415-003-1306-7.
50. de Lau, L. M. L.; Bornebroek, M.; Witteman, J. C. M.; Hofman, A.; Koudstaal, P. J.; Breteler, M. M. B. Dietary Fatty Acids and the Risk of Parkinson Disease: The Rotterdam Study. *Neurology* **2005**, *64* (12), 2040–2045. https://doi.org/10.1212/01.WNL.0000166038.67153.9F.
51. Gao, X.; Chen, H.; Fung, T. T.; Logroscino, G.; Schwarzschild, M. A.; Hu, F. B.; Ascherio, A. Prospective Study of Dietary Pattern and Risk of Parkinson Disease. *Am. J. Clin. Nutr.* **2007**, *86* (5), 1486–1494. https://doi.org/10.1093/ajcn/86.5.1486.
52. Miyake, Y.; Sasaki, S.; Tanaka, K.; Fukushima, W.; Kiyohara, C.; Tsuboi, Y.; Yamada, T.; Oeda, T.; Miki, T.; Kawamura, N.; et al. Dietary Fat Intake and Risk of Parkinson's Disease: A Case-Control Study in Japan. *J. Neurol. Sci.* **2010**, *288* (1–2), 117–122. https://doi.org/10.1016/j.jns.2009.09.021.
53. Pomponi, M.; Loria, G.; Salvati, S.; Di Biase, A.; Conte, G.; Villella, C.; Righino, E.; Ciciarelli, C.; Bria, P.; La Torre, G.; et al. DHA Effects in Parkinson Disease Depression. *Basal Ganglia* **2014**, *4* (2), 61–66. https://doi.org/10.1016/j.baga.2014.03.004.
54. Taghizadeh, M.; Tamtaji, O. R.; Dadgostar, E.; Daneshvar Kakhaki, R.; Bahmani, F.; Abolhassani, J.; Aarabi, M. H.; Kouchaki, E.; Memarzadeh, M. R.; Asemi, Z. The Effects of Omega-3 Fatty Acids and Vitamin E Co-Supplementation on Clinical and Metabolic Status in Patients with Parkinson's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. *Neurochem. Int.* **2017**, *108*, 183–189. https://doi.org/10.1016/j.neuint.2017.03.014.
55. Fernández-Sanz, P.; Ruiz-Gabarre, D.; García-Escudero, V. Modulating Effect of Diet on Alzheimer's Disease. *Dis. Basel Switz.* **2019**, *7* (1). https://doi.org/10.3390/diseases7010012.
56. Grimm, M. O. W.; Michaelson, D. M.; Hartmann, T. Omega-3 Fatty Acids, Lipids, and ApoE Lipidation in Alzheimer's Disease: A Rationale for Multi-Nutrient Dementia Prevention. *J. Lipid Res.* **2017**, *58* (11), 2083–2101. https://doi.org/10.1194/jlr.R076331.
57. Cunnane, S. C.; Plourde, M.; Pifferi, F.; Bégin, M.; Féart, C.; Barberger-Gateau, P. Fish, Docosahexaenoic Acid and Alzheimer's Disease. *Prog. Lipid Res.* **2009**, *48* (5), 239–256. https://doi.org/10.1016/j.plipres.2009.04.001.
58. Kalmijn, S.; Launer, L. J.; Ott, A.; Witteman, J. C.; Hofman, A.; Breteler, M. M. Dietary Fat Intake and the Risk of Incident Dementia in the Rotterdam Study. *Ann. Neurol.* **1997**, *42* (5), 776–782. https://doi.org/10.1002/ana.410420514.
59. Morris, M. C.; Evans, D. A.; Bienias, J. L.; Tangney, C. C.; Bennett, D. A.; Wilson, R. S.; Aggarwal, N.; Schneider, J. Consumption of Fish and N-3 Fatty Acids and Risk of Incident Alzheimer Disease. *Arch. Neurol.* **2003**, *60* (7), 940–946. https://doi.org/10.1001/archneur.60.7.940.
60. Huang, T. L.; Zandi, P. P.; Tucker, K. L.; Fitzpatrick, A. L.; Kuller, L. H.; Fried, L. P.; Burke, G. L.; Carlson, M. C. Benefits of Fatty Fish on Dementia Risk Are Stronger for Those without APOE Epsilon4. *Neurology* **2005**, *65* (9), 1409–1414. https://doi.org/10.1212/01.wnl.0000183148.34197.2e.
61. Schaefer, E. J.; Bongard, V.; Beiser, A. S.; Lamon-Fava, S.; Robins, S. J.; Au, R.; Tucker, K. L.; Kyle, D. J.; Wilson, P. W. F.; Wolf, P. A. Plasma Phosphatidylcholine Docosahexaenoic Acid Content and Risk of Dementia and Alzheimer Disease: The Framingham Heart Study. *Arch. Neurol.* **2006**, *63* (11), 1545–1550. https://doi.org/10.1001/archneur.63.11.1545.

62. Barberger-Gateau, P.; Raffaitin, C.; Letenneur, L.; Berr, C.; Tzourio, C.; Dartigues, J. F.; Alpérovitch, A. Dietary Patterns and Risk of Dementia: The Three-City Cohort Study. *Neurology* **2007**, *69* (20), 1921–1930. https://doi.org/10.1212/01.wnl.0000278116.37320.52.
63. Devore, E. E.; Grodstein, F.; van Rooij, F. J. A.; Hofman, A.; Rosner, B.; Stampfer, M. J.; Witteman, J. C. M.; Breteler, M. M. B. Dietary Intake of Fish and Omega-3 Fatty Acids in Relation to Long-Term Dementia Risk. *Am. J. Clin. Nutr.* **2009**, *90* (1), 170–176. https://doi.org/10.3945/ajcn.2008.27037.
64. Morris, M. C.; Tangney, C. C.; Wang, Y.; Sacks, F. M.; Bennett, D. A.; Aggarwal, N. T. MIND Diet Associated with Reduced Incidence of Alzheimer's Disease. *Alzheimers Dement. J. Alzheimers Assoc.* **2015**, *11* (9), 1007–1014. https://doi.org/10.1016/j.jalz.2014.11.009.
65. Freund-Levi, Y.; Eriksdotter-Jönhagen, M.; Cederholm, T.; Basun, H.; Faxén-Irving, G.; Garlind, A.; Vedin, I.; Vessby, B.; Wahlund, L.-O.; Palmblad, J. Omega-3 Fatty Acid Treatment in 174 Patients with Mild to Moderate Alzheimer Disease: OmegAD Study: A Randomized Double-Blind Trial. *Arch. Neurol.* **2006**, *63* (10), 1402–1408. https://doi.org/10.1001/archneur.63.10.1402.
66. Freund-Levi, Y.; Basun, H.; Cederholm, T.; Faxén-Irving, G.; Garlind, A.; Grut, M.; Vedin, I.; Palmblad, J.; Wahlund, L.-O.; Eriksdotter-Jönhagen, M. Omega-3 Supplementation in Mild to Moderate Alzheimer's Disease: Effects on Neuropsychiatric Symptoms. *Int. J. Geriatr. Psychiatry* **2008**, *23* (2), 161–169. https://doi.org/10.1002/gps.1857.
67. Chiu, C.-C.; Su, K.-P.; Cheng, T.-C.; Liu, H.-C.; Chang, C.-J.; Dewey, M. E.; Stewart, R.; Huang, S.-Y. The Effects of Omega-3 Fatty Acids Monotherapy in Alzheimer's Disease and Mild Cognitive Impairment: A Preliminary Randomized Double-Blind Placebo-Controlled Study. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2008**, *32* (6), 1538–1544. https://doi.org/10.1016/j.pnpbp.2008.05.015.
68. Quinn, J. F.; Raman, R.; Thomas, R. G.; Yurko-Mauro, K.; Nelson, E. B.; Van Dyck, C.; Galvin, J. E.; Emond, J.; Jack, C. R.; Weiner, M.; et al. Docosahexaenoic Acid Supplementation and Cognitive Decline in Alzheimer Disease: A Randomized Trial. *JAMA* **2010**, *304* (17), 1903–1911. https://doi.org/10.1001/jama.2010.1510.
69 Scheltens, P.; Kamphuis, P. J. G. H.; Verhey, F. R. J.; Olde Rikkert, M. G. M.; Wurtman, R. J.; Wilkinson, D.; Twisk, J. W. R.; Kurz, A. Efficacy of a Medical Food in Mild Alzheimer's Disease: A Randomized, Controlled Trial. *Alzheimers Dement. J. Alzheimers Assoc.* **2010**, *6* (1), 1-10.e1. https://doi.org/10.1016/j.jalz.2009.10.003.
70. Kamphuis, P. J. G. H.; Verhey, F. R. J.; Olde Rikkert, M. G. M.; Twisk, J. W. R.; Swinkels, S. H. N.; Scheltens, P. Efficacy of a Medical Food on Cognition in Alzheimer's Disease: Results from Secondary Analyses of a Randomized, Controlled Trial. *J. Nutr. Health Aging* **2011**, *15* (8), 720–724.
71. Scheltens, P.; Twisk, J. W. R.; Blesa, R.; Scarpini, E.; von Arnim, C. A. F.; Bongers, A.; Harrison, J.; Swinkels, S. H. N.; Stam, C. J.; de Waal, H.; et al. Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized, Controlled Trial. *J. Alzheimers Dis. JAD* **2012**, *31* (1), 225–236. https://doi.org/10.3233/JAD-2012-121189.
72. Shah, R. C.; Kamphuis, P. J.; Leurgans, S.; Swinkels, S. H.; Sadowsky, C. H.; Bongers, A.; Rappaport, S. A.; Quinn, J. F.; Wieggers, R. L.; Scheltens, P.; et al. The S-Connect Study: Results from a Randomized, Controlled Trial of Souvenaid in Mild-to-Moderate Alzheimer's Disease. *Alzheimers Res. Ther.* **2013**, *5* (6), 59. https://doi.org/10.1186/alzrt224.
73. Faxén-Irving, G.; Freund-Levi, Y.; Eriksdotter-Jönhagen, M.; Basun, H.; Hjorth, E.; Palmblad, J.; Vedin, I.; Cederholm, T.; Wahlund, L.-O. Effects on Transthyretin in Plasma and Cerebrospinal Fluid by DHA-Rich n - 3 Fatty Acid Supplementation in Patients with Alzheimer's Disease: The OmegAD Study. *J. Alzheimers Dis. JAD* **2013**, *36* (1), 1–6. https://doi.org/10.3233/JAD-121828.
74. Shinto, L.; Quinn, J.; Montine, T.; Dodge, H. H.; Woodward, W.; Baldauf-Wagner, S.; Waichunas, D.; Bumgarner, L.; Bourdette, D.; Silbert, L.; et al. A Randomized Placebo-Controlled Pilot Trial of Omega-3 Fatty Acids and Alpha Lipoic Acid in Alzheimer's Disease. *J. Alzheimers Dis. JAD* **2014**, *38* (1), 111–120. https://doi.org/10.3233/JAD-130722.
75. de Waal, H.; Stam, C. J.; Lansbergen, M. M.; Wieggers, R. L.; Kamphuis, P. J. G. H.; Scheltens, P.; Maestú, F.; van Straaten, E. C. W. The Effect of Souvenaid on Functional Brain Network Organisation in Patients with Mild Alzheimer's Disease: A Randomised Controlled Study. *PloS One* **2014**, *9* (1), e86558. https://doi.org/10.1371/journal.pone.0086558.
76. Phillips, M. A.; Childs, C. E.; Calder, P. C.; Rogers, P. J. No Effect of Omega-3 Fatty Acid Supplementation on Cognition and Mood in Individuals with Cognitive Impairment and Probable Alzheimer's Disease: A Randomised Controlled Trial. *Int. J. Mol. Sci.* **2015**, *16* (10), 24600–24613. https://doi.org/10.3390/ijms161024600.
77. Eriksdotter, M.; Vedin, I.; Falahati, F.; Freund-Levi, Y.; Hjorth, E.; Faxen-Irving, G.; Wahlund, L.-O.; Schultzberg, M.; Basun, H.; Cederholm, T.; et al. Plasma Fatty Acid Profiles in Relation to Cognition and Gender in Alzheimer's Disease Patients During Oral Omega-3 Fatty Acid Supplementation: The OmegAD Study. *J. Alzheimers Dis.* **2015**, *48* (3), 805–812. https://doi.org/10.3233/JAD-150102.

78. Wang, X.; Hjorth, E.; Vedin, I.; Eriksdotter, M.; Freund-Levi, Y.; Wahlund, L.-O.; Cederholm, T.; Palmblad, J.; Schultzberg, M. Effects of N-3 FA Supplementation on the Release of Proresolving Lipid Mediators by Blood Mononuclear Cells: The OmegAD Study. *J. Lipid Res.* **2015**, *56* (3), 674–681. https://doi.org/10.1194/jlr.P055418.
79. Olde Rikkert, M. G. M.; Verhey, F. R.; Blesa, R.; von Arnim, C. A. F.; Bongers, A.; Harrison, J.; Sijben, J.; Scarpini, E.; Vandewoude, M. F. J.; Vellas, B.; et al. Tolerability and Safety of Souvenaid in Patients with Mild Alzheimer's Disease: Results of Multi-Center, 24-Week, Open-Label Extension Study. *J. Alzheimers Dis. JAD* **2015**, *44* (2), 471–480. https://doi.org/10.3233/JAD-141305.
80. Jernerén, F.; Cederholm, T.; Refsum, H.; Smith, A. D.; Turner, C.; Palmblad, J.; Eriksdotter, M.; Hjorth, E.; Faxen-Irving, G.; Wahlund, L.-O.; et al. Homocysteine Status Modifies the Treatment Effect of Omega-3 Fatty Acids on Cognition in a Randomized Clinical Trial in Mild to Moderate Alzheimer's Disease: The OmegAD Study. *J. Alzheimers Dis. JAD* **2019**, *69* (1), 189–197. https://doi.org/10.3233/JAD-181148.
81. Scheltens, P.; Twisk, J. W. R.; Blesa, R.; Scarpini, E.; von Arnim, C. A. F.; Bongers, A.; Harrison, J.; Swinkels, S. H. N.; Stam, C. J.; de Waal, H.; et al. Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized, Controlled Trial. *J. Alzheimers Dis.* **2012**, *31* (1), 225–236. https://doi.org/10.3233/JAD-2012-121189.
82. Freund Levi, Y.; Vedin, I.; Cederholm, T.; Basun, H.; Faxén Irving, G.; Eriksdotter, M.; Hjorth, E.; Schultzberg, M.; Vessby, B.; Wahlund, L.-O.; et al. Transfer of Omega-3 Fatty Acids across the Blood-Brain Barrier after Dietary Supplementation with a Docosahexaenoic Acid-Rich Omega-3 Fatty Acid Preparation in Patients with Alzheimer's Disease: The OmegAD Study. *J. Intern. Med.* **2014**, *275* (4), 428–436. https://doi.org/10.1111/joim.12166.
83. Eriksdotter, M.; Vedin, I.; Falahati, F.; Freund-Levi, Y.; Hjorth, E.; Faxen-Irving, G.; Wahlund, L.-O.; Schultzberg, M.; Basun, H.; Cederholm, T.; et al. Plasma Fatty Acid Profiles in Relation to Cognition and Gender in Alzheimer's Disease Patients During Oral Omega-3 Fatty Acid Supplementation: The OmegAD Study. *J. Alzheimers Dis. JAD* **2015**, *48* (3), 805–812. https://doi.org/10.3233/JAD-150102.
84. Cummings, J.; Scheltens, P.; McKeith, I.; Blesa, R.; Harrison, J. E.; Bertolucci, P. H. F.; Rockwood, K.; Wilkinson, D.; Wijker, W.; Bennett, D. A.; et al. Effect Size Analyses of Souvenaid in Patients with Alzheimer's Disease. *J. Alzheimers Dis. JAD* **2017**, *55* (3), 1131–1139. https://doi.org/10.3233/JAD-160745.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

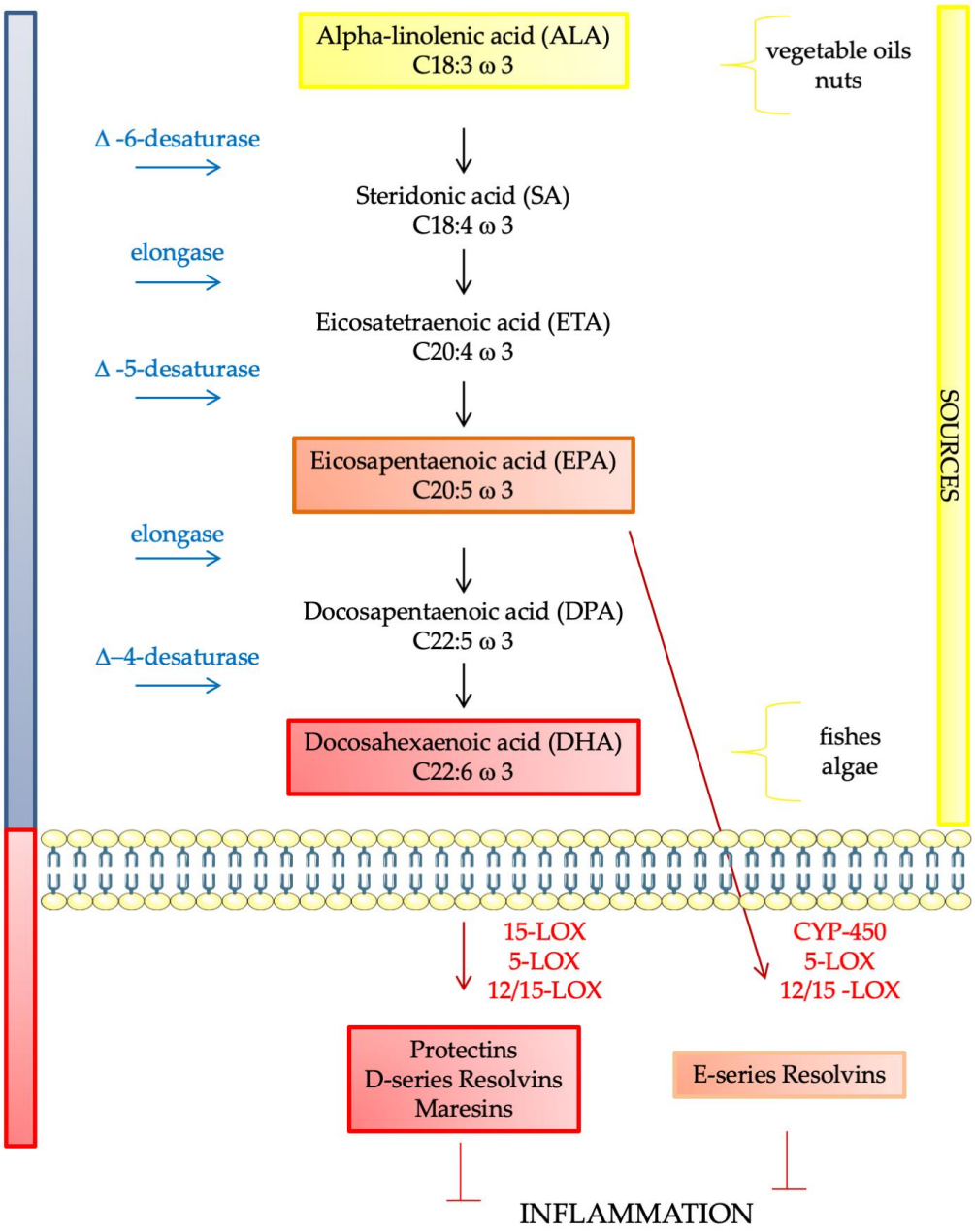

Figure 1. Endogenous synthesis of omega-3 polyunsaturated fatty acids and their involvement in inflammation. 15-LOX: 15-Lipoxygenase; 5-LOX: 5-Lipoxygenase; 12/15-LOX: 12/15 Lipoxygenase; CYP-450: Cytochrome P450.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 July 2019 doi:10.20944/preprints201907.0289.v1

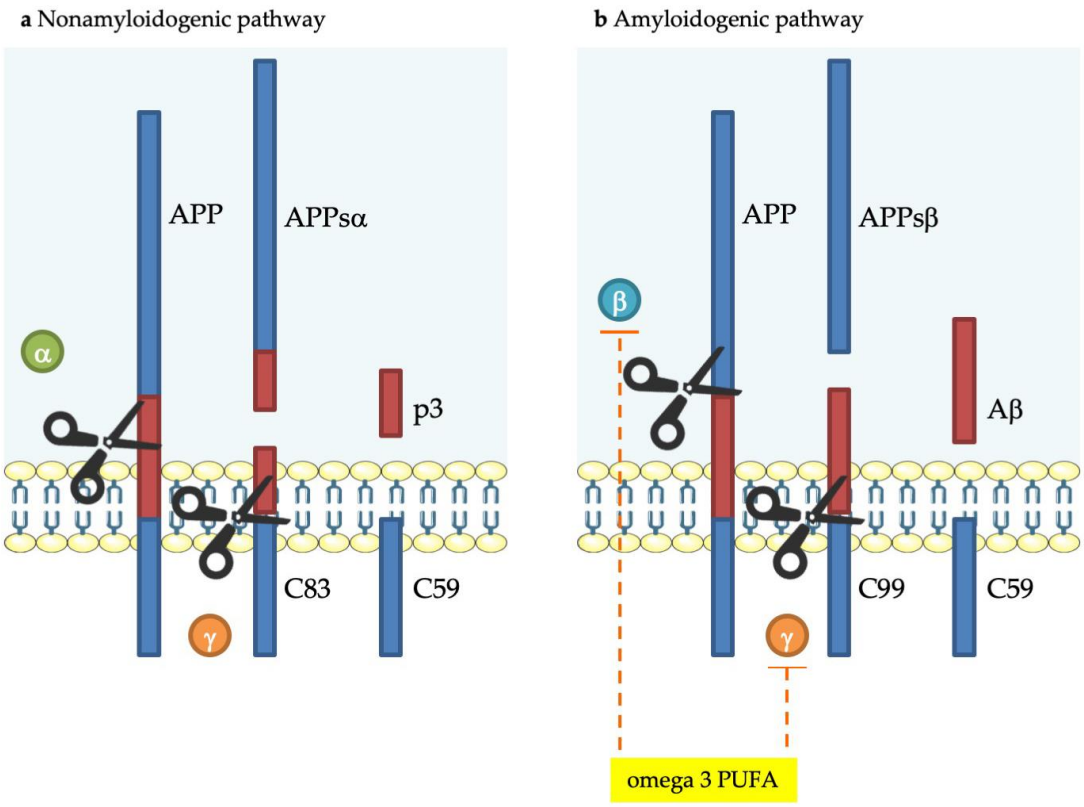

Figure 2. Amyloid precursor protein (APP) processing pathways. The non-amyloidogenic pathway (a) occurs upon sequential cleavage by α- and γ–secretases (non-pathological situation). The amyloidogenic pathway route (b) occurs when cleavage is carried out sequentially by β- and - γ secretases (pathological situation). Letters α, β, and γ represent each type of secretase. APP: amyloid precursor protein; APPsα: soluble α-APP; APPsβ: soluble β-APP. Omega-3 polyunsaturated fatty acids, proposed to inhibit APP processing, are shown in orange dashed lines.